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(21) International Application Number: PCT/US98/21392 (22) International Filing Date: 9 October 1998 (09.10.98) (30) Priority Data: 08/948,226 9 October 1997 (09.10.97) US (71) Applicant: MARS INCORPORATED [US/US]; 6885 Elm Street, McLean, VA 22101-3883 (US). (72) Inventors: ROMANCZYK, Leo, J., Jr.; 4 Fern Drive Road #3, Hackettstown, NJ 07840 (US). KOZIKOWSKI, Alan, P.; 45 Cameron Court, Princeton, NJ 08540 (US). TUECKMAN- TEL, Werner; Apartment #945, 2500 Wisconsin Avenue, N.W., Washington, DC 20007 (US). LIPPMAN, Marc, E.; 9220 Vendome Drive, Bethesda, MD 20817 (US). (74) Agents: KELLEY, Margaret B. et al.; Rogers & Wells, 200 Park Avenue, New York, NY 10166-0153 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: SYNTHETIC METHODS FOR POLYPHENOLS			
(57) Abstract  A process is disclosed for the production of polyphenol oligomers having n polyphenol monomeric units, n being an integer from 2-18. The process includes coupling of a protected polyphenol, having protected phenolic hydroxyl groups, which a C-4 functionalized polyphenol monomer. The protected polyphenol may be a protected polyphenol monomer or a protected polyphenol oligomer having 2-17 monomeric units. Advantageously, polyphenol monomeric units forming the polyphenol oligomers may be the same or different flavanoid compounds.			

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## TITLE

## SYNTHETIC METHODS FOR POLYPHENOLS

## BACKGROUND OF THE INVENTION

## Field of the Invention

This invention relates to synthetic polyphenol monomers and oligomers, derivatives thereof, and methods for making and using the same.

## Related Background Art

Polyphenols are a highly diverse group of compounds (Ferreira, D., Steynberg, J.P., Roux, D.G. and Brandt, E.V., *Tetrahedron*, 48, (10), 1743-1803 (1992)) which widely occur in a variety of plants, some of which enter into the food chain. In many cases, they represent an important class of compounds present in the human diet. Although some of the polyphenols are considered to be non-nutritive, interest in these

compounds has arisen because of their possible beneficial effects on health.

- For instance, quercetin (a flavonoid) has been shown to
- 5 possess anticarcinogenic activity in experimental animal studies (Deschner, E.E., Ruperto, J., Wong, G. and Newmark, H.L., *Carcinogenesis*, 7, 1193-1196 (1991) and Kato, R., Nakadate, T., Yamamoto, S. and Sugimura, T., *Carcinogenesis*, 4, 1301-1305 (1983)). (+)-Catechin
- 10 and (-)-epicatechin (flavan-3-ols) have been shown to inhibit Leukemia virus reverse transcriptase activity (Chu S.-C., Hsieh, Y.-S. and Lim, J.-Y., *J. of Natural Products*, 55, (2), 179-183 (1992)). Nobotanin (an oligomeric hydrolyzable tannin) has also been shown to
- 15 possess anti-tumor activity (Okuda T., Yoshida, T., and Hatano, T., *Molecular Structures and Pharmacological Activities of Polyphenols - Oligomeric Hydrolyzable Tannins and Others - Presented at the XVIth International Conference of the Groupe Polyphenols, Lisbon, Portugal, July 13-16, 1992*). Statistical
- 20 reports have also shown that stomach cancer mortality is significantly lower in the tea producing districts of Japan. Epigallocatechin gallate has been reported to be the pharmacologically active material in green
- 25 tea that inhibits mouse skin tumors (Okuda et al., *ibid.*). Ellagic acid has also been shown to possess anticarcinogen activity in various animal tumor models (Boukharta M., Jalbert, G. and Castonguay, A., *Efficacy of Ellagitannins and Ellagic Acid as Cancer*
- 30 *Chemopreventive Agents - Presented at the XVIth International Conference of the Groupe Polyphenols, Lisbon, Portugal, July 13-16, 1992*). Proanthocyanidin oligomers have been disclosed (JP 4-190774) by the Kikkoman Corporation for use as antimutagens. The use
- 35 of phenolic compounds in foods and their modulation of tumor development in experimental animal models has been recently presented at the 202nd National Meeting

and in vivo assessment of biological activities. For instance, anti-cancer activity is elicited by pentameric through decameric procyanidins, but not by monomers through tetrameric compounds. Currently, gram quantities of pure (>95%) pentamer are obtained by time-consuming methods which are not satisfactory for obtaining a sufficient quantity of the pentamer for large scale pharmacological and bioavailability studies. Even greater effort is required to obtain gram quantities of higher oligomers, hexamers through dodecamers, for similar studies since they are present in the natural product in much lower concentrations than the pentamer. Additionally, increasing oligomeric size increases structural complexity. Factors such as differences in the chirality of the monomeric units comprising the oligomer, different interflavan bonding sites, differences in the chirality of the interflavan bonding, dynamic rotational isomerization of the interflavan bonds, and the multiple points of bonding at nucleophilic centers pose efficiency constraints on current analytical methods of separation and purification for subsequent identification.

These collective factors point to a need for synthesis methods to permit the unambiguous proof of both structure and absolute configuration of higher oligomers, to provide large quantities of structurally defined oligomers for in vitro and in vivo assessment and to provide novel structural derivatives of the naturally occurring procyanidins to establish the structure-activity relationships of these materials. Accordingly, it would be advantageous to develop a versatile synthetic process capable of providing large quantities of any desired polyphenol oligomer.

of The American Chemical Society (Phenolic Compounds in Foods and Their Effects on Health I, Analysis, Occurrence & Chemistry, Ho, C.-T., Lee, C.Y., and Huang, M.-T editors, ACS Symposium Series 506, American Chemical Society, Washington, D.C. (1992); Phenolic Compounds in Foods and Their Effects on Health II. Antioxidants & Cancer Prevention, Huang, M.-T., Ho, C.-T., and Lee, C.Y. editors, ACS Symposium Series 507, American Chemical Society, Washington, D.C. (1992)).

10

Procyanidin polyphenols, and particularly higher oligomers thereof, have recently been found to possess a broad spectrum of biological activity. Reference is made to co-pending U.S. Patent Application No.

15 08/831,245, and corresponding International Application No. PCT/US97/05693, filed April 2, 1997, U.S. Patent Application No. 08/709,406, filed September 6, 1996, No. 08/631,661, and corresponding International Patent Application No. PCT/US96/04497, filed April 2, 1996,

20 now abandoned, and U.S. Patent Application No. 08/317,226, filed October 3, 1994, now U.S. Patent No. 5,554,645, each of which is incorporated herein by reference, that disclose the variety of health benefits

provided by procyanidin polyphenols as well as means of increasing the concentration of these beneficial polyphenols in extracts, foods, pharmaceutical preparations and chocolate compositions. Reference is

25 also made to parent application, U.S. Patent Application No. 08/948,226, filed October 9, 1997, which discloses methods of preparing polyphenol oligomers, and specifically procyanidin polyphenols, the disclosure of which is also incorporated herein by reference.

35 Isolation, separation, purification, and identification methods have been established for the recovery of a range of procyanidin oligomers for comparative *in vitro*



- 6 -

wherein

c is an integer from 1 to 3;

d is an integer from 1 to 4;

e is an integer from 0 to 2;

5 f is an integer from 0 to 2;

y is an integer from 2 to 6;

R<sup>1</sup> is H, OH or OR<sup>3</sup>;

R<sup>4</sup> is H or R<sup>5</sup>;

R, R<sup>2</sup> and R<sup>3</sup> are independently protecting groups;

10 and

R<sup>2</sup> is halo;

(c) coupling protected polyphenol monomer with the functionalized protected polyphenol monomer to  
15 produce a protected polyphenol dimer as the polyphenol oligomer, wherein the polyphenol monomeric units of the protected polyphenol monomer and the functionalized polyphenol monomer that comprise the oligomer are the same or different; and

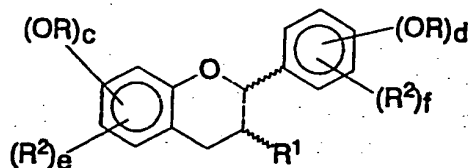
20 (d) optionally repeating the functionalization and coupling steps to form a polyphenol oligomer having n monomeric units, wherein n is an integer from 3 to 18. The halo group(s) of R<sup>2</sup>, when e + f is at least 2, may be the same or different, i.e. selected from the group  
25 consisting of chloro, fluoro, bromo, iodo.

The process of this invention also provides for the preparation of novel derivatives of the polyphenol oligomer. Halogenation of the functionalized protected  
30 polyphenol monomer provides a halogenated functionalized polyphenol monomer having the formula:

## SUMMARY OF THE INVENTION

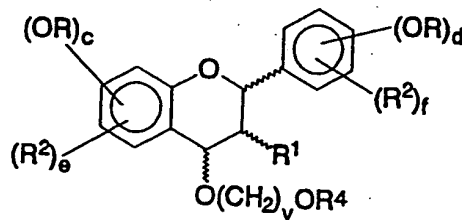
This invention is directed to a process for preparing a polyphenol oligomer comprised of coupled polyphenol monomeric, or flavanoid, units. The process of this invention comprises:

- (a) forming at least one protected polyphenol monomer by protecting each phenolic hydroxyl group of a polyphenol monomer with a protecting group having the formula:



- c is an integer from 1 to 3;  
 d is an integer from 1 to 4;  
 e is an integer from 0 to 2;  
 f is an integer from 0 to 2;  
 R<sup>1</sup> is H, OH or OR<sup>3</sup>;  
 R and R<sup>3</sup> are independently protecting groups; and  
 R<sup>2</sup> is halo;

- (b) functionalizing the 4-position of at least one protected polyphenol monomer to produce a functionalized protected polyphenol monomer having the formula:



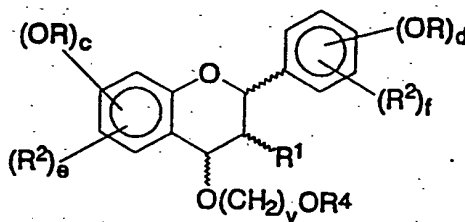
preparative HPLC), ED "synthetic epicatechin dimer (EC-(4 $\beta$ →8)-EC)), and EDDG (synthesized epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate) against the human breast cancer cell line MDA MB 231 at various  $\mu$ g/mL concentrations.

Fig. 1(b) is a bar graph showing the dose-response relationship between the control (solvent vehicle), monomer (epicatechin), pentamer (purified by preparative HPLC), ED (synthetic epicatechin dimer (EC-(4 $\beta$ →8)-EC)), and EDDG (synthesized epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate)) against the human breast cancer cell line MDA MB 435 at various  $\mu$ g/mL concentrations.

Fig. 1(c) is a bar graph showing the dose-response relationship between the control (solvent vehicle), monomer (epicatechin), EGCG (epigallocatechin gallate from Sigma), ED (synthesized epicatechin dimer (EC-(4 $\beta$ →8)-EC)), EDDG (synthesized epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate)), ECDD (repeated synthesis of epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate)), and ECTT (synthesized epicatechin trimer trisgallate ([EC-3-O-galloyl-(4 $\beta$ →8)],-EC-3-O-gallate)) against the human breast cancer cell line MDA 231 at various  $\mu$ g/mL concentrations.

Fig. 1(d) is a bar graph showing the dose-response relationship between the control (solvent vehicle), monomer (epicatechin), EGCG (epigallocatechin gallate from Sigma), ED (synthesized epicatechin dimer (EC-(4 $\beta$ →8)-EC)), EDDG (synthesized epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate)), ECDD (repeated synthesis of epicatechin dimer bisgallate (EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate)), and ECTT (synthesized epicatechin trimer trisgallate

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wherein, c is an integer from 1 to 3, d is an integer from 1 to 4, e is an integer from 0 to 2, f is an integer from 0 to 2, y is an integer from 2 to 6, R<sup>1</sup> is H, OH or OR<sup>3</sup>, R<sup>4</sup> is H or R<sup>5</sup>, R, R<sup>3</sup> and R<sup>5</sup> are independently protecting groups, and R<sup>2</sup> is halo, wherein if e + f is at least 2 the halo substituent may be the same or different. This halogenated functionalized monomer may be used for the production of a halogenated polyphenol oligomer by coupling of this monomer with either a protected polyphenol monomer or with a protected polyphenol oligomer. Alternatively, halogenated polyphenol oligomers may be prepared by direct halogenation of the polyphenol oligomer.

Other novel derivatives may be prepared by esterifying or glycosylating the polyphenol oligomer to produce a derivatized polyphenol oligomer. Formation of the derivatized oligomers may be conducted either prior to or subsequent to removal of the protecting groups from the phenolic hydroxyl groups of the polyphenol oligomer. Accordingly, this invention is also directed to novel polyphenol monomers, novel polyphenol oligomers, and novel polyphenol monomer and oligomer derivatives.

#### BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1(a) is a bar graph showing the dose-response relationship between the control (solvent vehicle), monomer (epicatechin), pentamer (purified by

R' is H or OH.

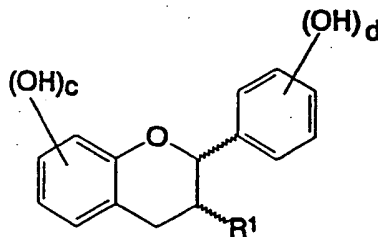
The polyphenol monomer may contain additional substituents, or derivatives of the hydroxyl substituents, as described below. The term polyphenol oligomer means a polymer composed of a series of polyphenol monomeric units that may possess the same or different flavanoid structures: The polyphenol monomeric units are the polyphenol monomers that have been coupled or bonded together to form an oligomer. The term polyphenol(s) includes proanthocyanidins, and derivatives thereof, and specifically includes procyanidins, such as those that can be extracted from cocoa beans, and derivatives thereof, as well as structurally similar synthetic materials.

(([EC-3-O-galloyl(4 $\beta$ -8)]<sub>2</sub>-EC-3-O-gallate)) against the human breast cancer cell line MCF-7 at various  $\mu\text{g/mL}$  concentrations.

5 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process of synthesizing polyphenol oligomers and derivatives thereof. The subject compounds of the invention have  
10 the same uses, and are formulated, purified and administered in the same manner as described in U.S. Patent Application No. 08/831,245 filed April 2, 1997. Accordingly, the compounds of this invention may be used, for example, as antineoplastic agents,  
15 antioxidants, DNA topoisomerase II enzyme inhibitors, cyclo-oxygenase and/or lipoxygenase modulators, nitric oxide of nitric oxide-synthase modulators, as non-steroidal anti-inflammatory agents, antimicrobial agents, apoptosis modulators, platelet aggregation  
20 modulators, glucose modulators, and inhibitors of oxidative DNA damage.

As used herein, the term polyphenol monomer means a polyhydroxy-substituted compound having the following  
25 flavanoid based structure:

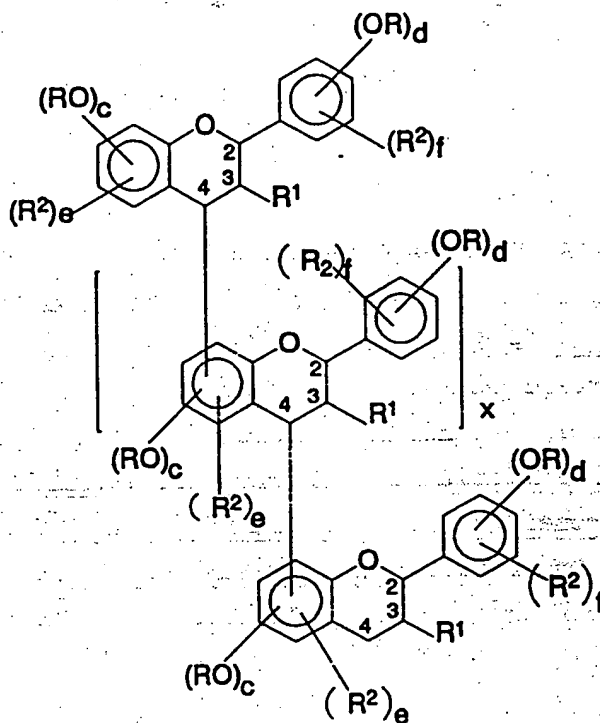


wherein

c is an integer from 1 to 3;

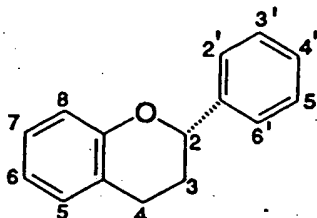
d is an integer from 1 to 4;

In a preferred embodiment, the present invention provides a process of synthesizing polyphenol oligomers of the formula:



5 or

Representative proanthocyanidins include:



			Substitution Pattern						
	Class	Monomer	3	5	7	8	3'	4'	5'
5	Proapigeninidin	Apigeniflavan	H	OH	OH	H	H	OH	H
	Proluteolinidin	Luteoliflavan	H	OH	OH	H	OH	OH	H
	Protricetinidin	Tricetiflavan	H	OH	OH	H	OH	OH	OH
	Propelargonidin	Afzelechin	OH	OH	OH	H	H	OH	H
10	Procyanidin	Catechin	OH	OH	OH	H	OH	OH	H
	Prodelphinidin	Gallocatechin	OH	OH	OH	H	OH	OH	OH
	Proguibourtinidin	Guibourtinidol	OH	H	OH	H	H	OH	H
	Profisetinidin	Fisetinidol	OH	H	OH	H	OH	OH	H
	Prorobinetinidin	Robinetinidol	OH	H	OH	H	OH	OH	OH
15	Proteracacinidin	Oritin	OH	H	OH	OH	H	OH	H
	Promelacacinidin	Prosopin	OH	H	OH	OH	OH	OH	H

20 The present invention provides a process of preparing substantially pure polyphenol oligomers, and derivatives thereof.



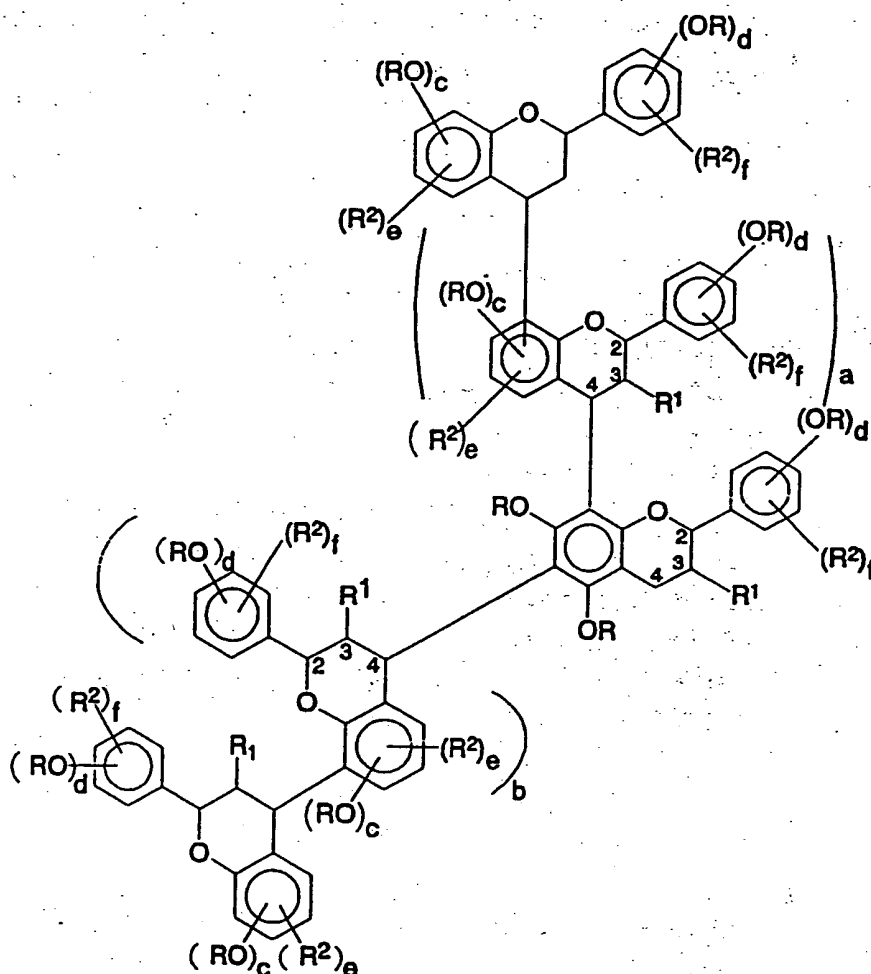
or d is 2 and are adjacent, methylene, diphenylmethylene or substituted diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group  
5 consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkoxy; and

R<sup>1</sup> is hydrogen, hydroxy, an -O-glycoside, an -O-substituted glycoside, -OC(O)-aryl,  
10 -OC(O)-substituted aryl, -OC(O)-styryl, or -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, or -C(O)-substituted styryl; wherein said substituted aryl  
15 or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, aryl, amino, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy;

20 R<sub>2</sub> is halo; and R<sup>2</sup> is halo, wherein if e + f is at least 2 the halo substituent may be the same or different; and

wherein said process comprises the steps of  
subjecting a first polyphenol monomer to conditions  
25 sufficient to produce a C-4 functionalized polyphenol monomer and coupling that C-4 functionalized monomer with a second polyphenol monomer or an oligomer having up to 17 monomeric units that are the same or different. The first and second polyphenol monomers  
30 may be the same or different.

The process of the present invention may be used to prepare substantially pure polyphenol oligomers, and derivatives thereof. The oligomeric compounds are  
35 comprised of n polyphenol monomeric units, wherein n is an integer of 2 through 18, preferably 2 through 5, or 4 through 12, more preferably n is 3 through 12, and



wherein

x is an integer from 0 to 16;

a is an integer from 1 to 15;

5 b is an integer from 1 to 15;

the sum  $a + b$  is an integer from 2 to 17;

c is independently an integer from 1 to 3;

d is independently an integer from 1 to 4;

e is independently an integer from 0 to 2;

10 f is independently an integer from 0 to 2;

R is independently hydrogen,  $C_1$ - $C_4$  alkyl, benzyl, substituted benzyl, or a silyl moiety containing  $C_1$ - $C_4$  alkyl or aryl substituents, or, when c

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produce the polyphenol oligomer, wherein the oligomer is a protected polyphenol dimer.

The polyphenol dimer thus produced is composed of the coupled first and second monomers, as the first and second monomeric units. The functionalization and coupling steps may be repeated to form polyphenol oligomers, wherein the oligomers may be comprised of  $n$  monomers, and  $n$  is an integer from 3 to 18.

10 Preferably,  $n$  is an integer from 5-12.

Accordingly, the process described above may be continued by:

- (a) functionalizing the 4-position of a third protected polyphenol monomer to produce a third functionalized polyphenol monomer;
- (b) coupling the functionalized third polyphenol monomer with the protected polyphenol dimer to produce a protected polyphenol trimer;
- 20 (c) optionally repeating the functionalization and coupling steps to form a polyphenol oligomer comprised of  $n$  monomers, wherein  $n$  is an integer from 4 to 18. The first, second and third polyphenol monomers may possess the same or different flavanoid structures.

25 Suitable protecting groups used in the process of this invention include those protecting groups that may be introduced and removed from the polyphenol monomers and oligomers without racemization or degradation of the monomers or oligomers and that are stable to the conditions used for functionalizing and coupling reactions. Methods for protecting and de-protecting hydroxyl groups are well known to those skilled in the art and are described in "Protective Groups in Organic

30 Synthesis" T.W. Greene, John Wiley & Sons. Preferably, the protecting groups used in the process of this invention to protect the phenolic hydroxyl groups of

- 15 -

most preferably n is 5 through 12, and having linkages of 4→6 and 4→8. The polyphenol oligomers prepared by the processes of this invention may be represented by the formula above, wherein x is 0 through 16, and  
5 higher. When x is 0, the oligomer is termed a "dimer"; when x is 1, the oligomer is termed a "trimer"; when x is 2, the oligomer is termed a "tétramer"; when x is 3, the oligomer is termed a "pentamer"; and similar recitations may be designated for oligomers having x up  
10 to and including 16 and higher, such that when x is 16, the oligomer is termed an "octadecamer".

Linear and branched polyphenol oligomers may be prepared by the process of the present invention using  
15 a sequence comprising protection, functionalization, coupling and deprotection reactions. In each reaction sequence, any polyphenol monomer, as exemplified above, may be used to prepare linear or branched oligomers containing monomeric units of the same polyphenol  
20 monomer or of different polyphenol monomers. Higher oligomers may be prepared by repeating the coupling step by coupling a dimer, trimer, or higher oligomer with additional monomer.

25 Generally, the process for the production of polyphenol oligomers comprises the steps of:

(a) protecting each phenolic hydroxyl group of at least a first and second polyphenol monomer using a suitable phenol protecting group to provide at least a  
30 first and a second protected polyphenol monomer, wherein the first and second polyphenol monomers may be the same or different flavanoid compounds;

(b) functionalizing the 4-position of the first protected polyphenol monomer to produce a  
35 functionalized polyphenol monomer;

(c) coupling the functionalized polyphenol monomer with the second protected polyphenol monomer to

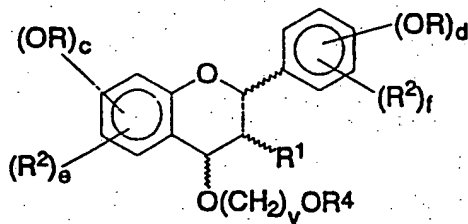
(a) protecting each phenolic hydroxyl group of a first and second polyphenol monomer using a suitable phenol protecting group to provide a first and a second protected polyphenol monomer, wherein the first and second polyphenol monomers may be the same or different flavanoid compounds;

(b) oxidatively functionalizing the 4-position of the first protected polyphenol monomer using an oxidizing agent to provide a 4-functionalized protected polyphenol monomer;

(c) coupling the second protected polyphenol monomer and the functionalized polyphenol monomer using a catalyst to provide a polyphenol oligomer; and

(d) optionally deprotecting the polyphenol oligomer to provide an unprotected polyphenol oligomer.

The oxidative functionalization of the 4-position of a protected polyphenol monomer produces a functionalized protected polyphenol monomer having the formula:



wherein

c is an integer from 1 to 3;

d is an integer from 1 to 4;

e is an integer from 0 to 2;

f is an integer from 0 to 2;

y is an integer from 2 to 6;

R<sup>1</sup> is H, OH or OR<sup>3</sup>;

R<sup>4</sup> is H or R<sup>5</sup>;

R, R<sup>3</sup> and R<sup>5</sup> are independently protecting

groups; and

R<sup>2</sup> is halo.

the polyphenol monomers include benzyl, C<sub>1</sub>-C<sub>6</sub> alkyl, substituted benzyl, alkyl silyl, aryl silyl, or substituted aryl silyl containing C<sub>1</sub>-C<sub>6</sub> alkyl, aryl or substituted aryl substituents, wherein the substituted benzyl protecting group or substituted aryl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy. When the polyphenol monomer contains two phenolic hydroxyl groups that are adjacent, the protecting group may be methylene, diphenylmethylene or substituted diphenylmethylene, wherein each of the substituted phenyl groups of the diphenylmethylene protecting group may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy.

As used herein, aryl means an aromatic hydrocarbon compound selected from the group consisting of phenyl, substituted phenyl, naphthyl, or substituted naphthyl, wherein the substituted phenyl or substituted naphthyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy.

The protecting group may be removed from the phenolic hydroxyl groups of the polyphenol oligomer to produce an unprotected polyphenol oligomer. In addition, the protected or unprotected polyphenol oligomer may be derivatized to produce derivatized polyphenol oligomers.

Preferably, the process of the present invention comprises:

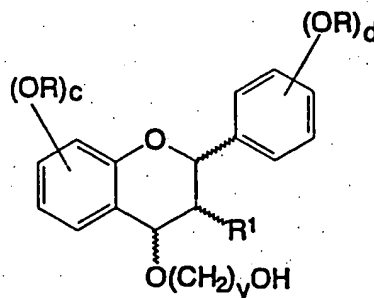
catalysts that are useful in the present invention include titanium tetrahalides (e.g. titanium tetrachloride), aluminum trihalides (e.g. aluminum trichloride), boron trihalides (e.g. boron trifluoride etherate), trialkyl or triaryl silyl compounds (e.g. trimethyl silyl triflate) and the like.

Exemplary oxidizing agents useful in the process of this invention include quinone-type oxidizing agents and metal acetate oxidizing agents (e.g. lead tetraacetate).

Preferably, the process of the present invention comprises:

(a) protecting each phenolic hydroxyl group of a first and a second polyphenol monomer using a benzyl-ether protecting group to produce a first and a second protected polyphenol monomer, wherein the first and second polyphenol monomers may be the same or different flavanoid compounds;

(b) oxidatively functionalizing the 4-position of the first protected polyphenol monomer using a quinone oxidizing agent in the presence of an alcohol, preferably a diol, to provide a 4-alkoxy functionalized protected polyphenol monomer having the formula:



wherein

c is an integer from 1 to 3;

d is an integer from 1 to 4;

When e or f are 1 or 2, functionalization of the monomer preferably precedes introduction of the halo substituent.

- 5 An important transformation in the process of the present invention is the formation of the oxidatively functionalized protected polyphenol monomer used in the oligomer-forming coupling reaction. It has been determined that high purity of this monomer is
- 10 important for obtaining oligomeric products in good purity. Advantageously, it has been discovered that formation of the 4-alkoxy polyphenol monomer using ethylene glycol, in place of lower alkyl alcohols, provides a functionalized polyphenol monomer that may
- 15 be readily purified by chromatography. Use of methanol, ethanol, or even isopropyl alcohol, provides 4-alkoxy polyphenol monomers that are not separable or difficult to separate chromatographically from the non-oxidized phenol and from by-products and cannot be
- 20 used satisfactorily in the oligomer-forming coupling reaction. Accordingly, another aspect of the present invention comprises providing a substantially pure 4(2-hydroxyethyl) functionalized polyphenol monomer useful for forming polyphenol oligomers. A preferred quinone-
- 25 type oxidizing agent is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

- Another important transformation in the process of this invention is the coupling of the oxidatively
- 30 functionalized polyphenol monomer to a protected polyphenol monomer or a protected polyphenol oligomer. The coupling reaction is conducted using a protic acid catalyst or a Lewis acid catalyst. Hydrochloric acid (HCl) is an exemplary protic acid that may be used as a
- 35 catalyst in the process of this invention. A particularly useful form of hydrochloric acid is as an anhydrous solution in dioxane. Exemplary Lewis Acid



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- (c) coupling the first protected polyphenol monomer and the second functionalized protected polyphenol monomer using titanium tetrachloride to provide a polyphenol oligomer; and
- 5 (d) deprotecting the polyphenol oligomer to provide an unprotected polyphenol oligomer.

The processes of this invention also provides for the preparation of novel derivatized oligomers, wherein at

10 least one unprotected hydroxyl group of the polyphenol oligomer is derivatized using standard esterification or glycosylation techniques to form an ester or glycosyl ether derivative, respectively. Accordingly, this invention is directed to a process for the

15 production of a derivatized polyphenol oligomer, which comprises esterifying a protected polyphenol oligomer, wherein each phenolic hydroxyl group of the polyphenol oligomer is protected, to produce a protected esterified polyphenol oligomer, and to a process which

20 comprises esterifying an unprotected polyphenol oligomer to produce an esterified polyphenol oligomer. Optionally, the protecting groups of the protected esterified polyphenol oligomer may be removed to provide an esterified polyphenol oligomer. This

25 invention is also directed to a process for the production of a derivatized polyphenol oligomer, which comprises glycosylating the polyphenol oligomer, that is forming a glycosyl ether derivative of the oligomer, wherein each phenolic hydroxyl group of the polyphenol

30 oligomer is protected, to produce a protected glycosylated polyphenol oligomer, and to a process which comprises glycosylating an unprotected polyphenol oligomer to produce a glycosylated polyphenol oligomer. Optionally, the protecting groups of the protected

35 glycosylated polyphenol oligomer may be removed to provide a glycosylated polyphenol oligomer. In addition, ester derivatives of the glycosyl ethers may

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y is an integer from 2 to 6;  
 R is a protecting group; and  
 R' is H or OH;

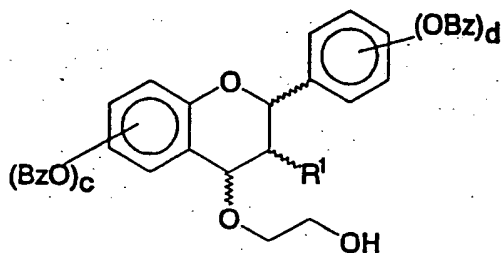
5 (c) coupling the second protected polyphenol monomer and the functionalized polyphenol monomer using a protic acid catalyst or a Lewis Acid catalyst to provide a polyphenol oligomer; and

(d) deprotecting the polyphenol oligomer to  
 10 provide an unprotected polyphenol oligomer.

More preferably, the process of the present invention comprises:

(a) protecting each phenolic hydroxyl group of  
 15 a first and a second polyphenol monomer using a benzyl ether protecting group to produce a first and a second protected polyphenol monomer;

(b) oxidatively functionalizing the 4-position  
 of the second protected polyphenol monomer using  
 20 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the presence of ethylene glycol to provide a 4-functionalized protected polyphenol monomer having the formula:



25 wherein

c is an integer from 1 to 3;

d is an integer from 1 to 4;

R' is H or OH; and

Bz represents a benzyl moiety

30

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- hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy. Preferably, the ester moiety, -C(O)-substituted aryl
- 5 and -C(O)-substituted styryl, is derived from an acid selected from the group consisting of caffeic, cinnamic, coumaric, ferulic, gallic, hydroxybenzoic and sinapic acids.
- 10 Additionally, polyphenol oligomers, comprised of 2 to 18 monomeric units, may be glycosylated to provide glycosylated polyphenol oligomers, wherein the 3-hydroxyl group on at least one monomeric unit of the oligomer is converted to a glycosyl ether, wherein the
- 15 glycosyl moiety may be an -O-glycoside or an -O-substituted glycoside, wherein the substituted glycoside is substituted by -C(O)aryl, -C(O)-substituted aryl, -C(O)-styryl, or -C(O)-substituted styryl; wherein said substituted aryl
- 20 or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy. Preferably, the
- 25 glycoside moiety is derived from a sugar selected from the group consisting of glucose, galactose, xylose, rhamnose and arabinose.

- Another embodiment of this invention provides a process
- 30 for halogenating the protected polyphenol monomers, functionalized protected polyphenol monomers and polyphenol oligomers prepared according the process of this invention. A halogenated polyphenol monomer having the formula:

be prepared by esterifying at least one hydroxyl group of the glycosyl moiety.

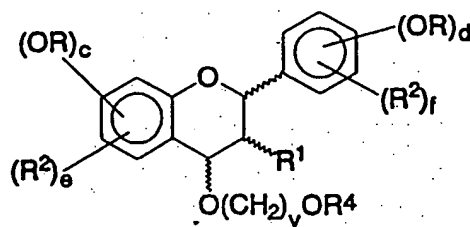
Polyphenol oligomer ester derivatives may be prepared by treatment of the oligomer having a reactive hydroxyl moiety with an activated acid. As used herein, an activated acid is an organic acid having a carboxyl moiety that is activated toward reaction with an hydroxyl moiety. The activated acid may be a compound that can be isolated, such as an acid chloride, an acid anhydride, a mixed acid anhydride and the like, or may be formed *in situ*, for example by treatment of an acid with dicyclohexyl carbodiimide (DCC), carbonyl di-imidazole, and the like.

Polyphenol oligomer glycosides may be prepared by the methods described in Toshima, K.,; Tatsuta, K. *Chem. Rev.*, 93, 1503-1531 (1993), Igarashi, K. *Adv. Carbohydr. Chem. Biochem.*, 34, 243 (1977) and D. Kahne et al., *J. Am. Chem. Soc.*, 11, 6881 (1989), or by treatment of a monomer using cyclodextrin glucanotransferase (EC 2.4.1.19, CGTase) according to the procedures described by Funayama et al. to produce a monomer glucoside (M. Funayama, H. Arakawa, R. Yamamoto, T. Nishino, T. Shin and S. Murao, *Biosci. Biotech. Biochem.*, 58, (5), 817-821 (1994)).

According to the process of this invention, polyphenol oligomers, comprised of 2 to 18 monomeric units, may be esterified to provide an esterified polyphenol oligomer, wherein the 3-hydroxyl group on at least one monomeric unit of the oligomer is converted to an ester, wherein the ester moiety may be -OC(O)aryl, -OC(O)-substituted aryl, -OC(O)-styryl, -OC(O)-substituted styryl; wherein said substituted aryl or substituted styryl contains at least one substituent selected from the group consisting of halo,

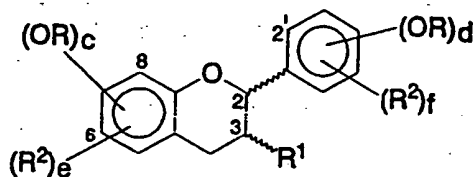
the disclosure of which is incorporated herein by reference.

In yet another embodiment of this invention, a  
 5 halogenated functionalized polyphenol monomer having the formula:



wherein

- 10 c is an integer from 1 to 3;  
 d is an integer from 1 to 4;  
 e is an integer from 0 to 2;  
 f is an integer from 0 to 2;  
 y is an integer from 2 to 6;  
 15 R<sup>1</sup> is H, OH or R<sup>3</sup>;  
 R<sup>4</sup> is H or R<sup>5</sup>;  
 R, R<sup>3</sup> and R<sup>5</sup> are independently protecting groups; and  
 R<sup>2</sup> is halo;  
 20 may be prepared by the process of treating a functionalized polyphenol monomer, wherein e and f are 0, with a halogenating agent for a time and at a temperature sufficient to effect the halogenation of the monomer. The halo group(s) of R<sup>2</sup>, when e + f is at least 2, may be the same or different, i.e. selected from the group consisting of chloro, fluoro, bromo, iodo. Advantageously, different halogen substituents may be introduced into the polyphenol monomer. For  
 25 example, a polyphenol monomer may be subjected to a first halogenation to introduce a halogen substituent,



wherein

- c is an integer from 1 to 3;
- d is an integer from 1 to 4;
- e is an integer from 0 to 2;
- f is an integer from 0 to 2;
- R and R<sup>3</sup> are independently a protecting group;
- R<sup>1</sup> is H, OH or OR<sup>3</sup>; and
- R<sup>2</sup> is halo;

may be prepared by the process of treating a polyphenol monomer, wherein e and f are 0, with a halogenating agent for a time and at a temperature sufficient to effect the halogenation of the monomer. The halo group may be chloro, bromo, fluoro, iodo or mixtures thereof. The bromo group is most preferred. Exemplary halogenating agents that may be useful in the process of this invention include, N-bromosuccinimide, acetyl hypofluorite, cesium fluoroxysulfate, trifluoromethyl hypofluorite, N-fluoropyridinium salts, 1-chloromethyl-4-fluoro-1,4 diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), sulfuryl chloride/diphenylsulfide (in the presence of a Lewis Acid), sodium, calcium, or tert-butyl hypochlorite, trimethyl(phenyl)ammonium tetrachloriodate (III), tetraethylammonium trichloride, iodine/periodic acid, iodine/bis(trifluoroacetoxy)iodobenzene, iodine/copper(II)acetate, iodine/silver sulfate, benzyl trimethylammonium dichloriodate(I) and the like.

Other brominating agents of catechins are described in Ballenegger et al., (Zyma SA) European Patent 0096 007,

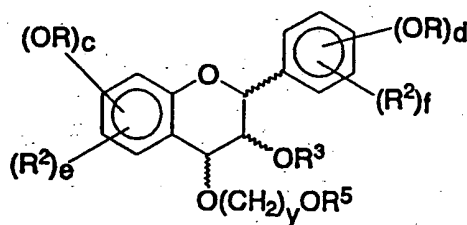
of the protecting group may be accomplished without removal of the halogen substituent. For example, hydrogenolysis, used to remove benzyl protecting groups, of a benzylated-brominated monomer, will both  
5 de-benzylate and de-brominate a monomer or an oligomer. The skilled artisan will recognize that the protecting group(s) and halogen substituent(s) may be selected such that these groups may advantageously be removed or retained during the protection, halogenation, coupling  
10 and de-protection steps.

Limitation of the amount of halogenating agent used during the halogenation reaction will provide for the selective formation of mono-, di-, tri- or tetra-  
15 halogenated polyphenol monomers. According to the process of this invention, use of approximately one equivalent of halogenating agent provides for the formation of mono-halogenated monomers, whereas use of  
20 3 equivalents halogenating agent provides for the preparation of tri-bromo protected polyphenol monomers and tri-bromo functionalized protected polyphenol monomers.

The regiochemistry of the halogenation is dependent  
25 upon the substitution pattern of the starting polyphenol monomer, specifically, the hydroxyl-substitution pattern starting flavanoid compound. For example, mono-bromination of protected polyphenol monomers, (+)-catechin or (-)-epicatechin, provides for  
30 the preparation of the 8-bromo derivatives of these flavanoids. Di-bromination of the protected (+)-catechin or (-)-epicatechin, provides for the preparation of 6,8-dibromo products. Tri-bromination of the protected (+)-catechin or (-)-epicatechin,  
35 provides for the preparation of 6,8,6'-tribromo products. Accordingly, the process of this invention provides that any and all of the polyphenol monomers or

so that for  $(R^2)_e$ , e is 1 and  $R_2$  is bromo. This halogenated monomer may then be subjected to a second halogenation to introduce a different halogen substituent, so that for  $(R^2)_e$ , e is 2 and  $R_2$  is bromo and fluoro. Similarly, halogenation may be conducted to introduce different halogen substituents at  $(R_2)_f$ .

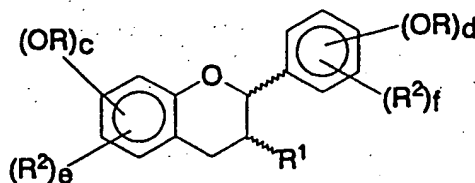
Alternatively, one or both of the alkoxy-hydroxyl groups of the functionalized polyphenol monomer may be protected with protecting groups,  $R^3$  or  $R^5$ , prior to halogenation, to provide a monomer having the following formula:



Exemplary alcohol-hydroxyl protecting groups are the same protecting groups (R), described above, that are useful for protecting the phenolic hydroxyl moieties. The protecting group that may be used to protect the alcohol-hydroxyl moieties ( $R^3$  or  $R^5$ ) may be the same as or different than the protecting group used to protect the phenolic hydroxyl moieties (R). Preferably, the alcohol-hydroxyl moiety at the 3-position of the polyphenol monomer may be protected using an alkyl silyl protecting group, preferably a tert-butyl-dimethylsilyl protecting group. Optionally, the alcohol-hydroxyl protecting groups(s) may be removed from the functionalized polyphenol monomer after halogenation or removed after coupling to another monomer or oligomer. Most preferably, the alcohol-hydroxyl protecting group is selected such that removal



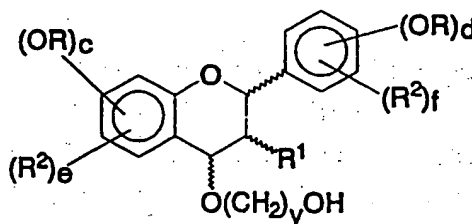
- 30 -



wherein

- 5           c is an integer from 1 to 3;  
             d is an integer from 1 to 4;  
             e is an integer from 0 to 2;  
             f is an integer from 0 to 2;

and



10

wherein

- c is an integer from 1 to 3;  
             d is an integer from 1 to 4;  
             e is an integer from 0 to 2;  
 15           f is an integer from 0 to 2;  
             y is an integer from 2 to 6;

and, for each of the above,

- R is C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, substituted benzyl,  
             C<sub>1</sub>-C<sub>4</sub> alkyl, and a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or  
 20           aryl substituents, or, when c or d is 2 and are  
             adjacent, methylene, diphenylmethylene or substituted  
             diphenylmethylene, wherein said substituted benzyl or  
             each substituted phenyl may contain substituents  
             selected from the group consisting of halo, nitro,  
 25           cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy  
             C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkoxy;

oligomers described herein, may optionally be subjected to halogenation to form novel halogenated polyphenol monomers or oligomers.

- 5 A mono-, di- or tri-halogenated functionalized protected polyphenol monomer may be coupled with a protected polyphenol monomer or with a protected polyphenol oligomer to produce a novel halogenated polyphenol oligomer using any of the above described
- 10 procedures. Coupling of the halogenated functionalized protected polyphenol monomer with a halogenated protected polyphenol monomer or with a halogenated protected polyphenol oligomer produces other novel halogenated polyphenol oligomers. Coupling of the
- 15 halogenated functionalized monomer with an 8-halogenated protected polyphenol monomer or oligomer produces ( $4\alpha \rightarrow 6$ ) or ( $4\beta \rightarrow 6$ ) coupled, or branched oligomers. Formation of these branched compounds may be accomplished only when the protecting groups on the
- 20 phenolic hydroxyl groups of the halogenated protected monomer or halogenated protected oligomer do not prevent reaction due to steric hinderance. For example, when sterically large protecting groups, such as benzyl, are present on the halogenated protected
- 25 polyphenol monomer, coupling will not occur. Whereas, coupling of unprotected polyphenols will provide branched compounds. Preferably, the halogenated polyphenol compounds produced herein are brominated polyphenol compounds. Alternatively, halogenated
- 30 polyphenol oligomers may also be prepared by direct halogenation of a selected polyphenol oligomer.

A further embodiment of this invention are derivatized or underivatized halogenated polyphenol monomers having

35 the formula:

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R<sup>1</sup> is hydrogen, hydroxy, an -O-glycoside, an -O-substituted glycoside, -OC(O)-aryl, -OC(O)-substituted aryl, -OC(O)-styryl, -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, -C(O)-substituted styryl; and

R<sup>2</sup> is halo;

wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and C<sub>3</sub>-C<sub>8</sub> cycloalkoxy.

15

Accordingly, yet another embodiment of the invention is directed to a process for the production of a polyphenol oligomer by coupling of polyphenol monomers, wherein each phenolic hydroxyl group of the polyphenol monomer is protected, comprising the steps of:

20

(a) functionalizing the 4-position of a first protected polyphenol monomer to produce functionalized polyphenol monomer;

25

(b) substituting the 6- or 8-position of a protected polyphenol, wherein the polyphenol is a protected monomer or a protected oligomer, to produce a blocked polyphenol; and

30

(c) coupling said functionalized polyphenol monomer with said blocked polyphenol to form the polyphenol oligomer.

Advantageously, the 8-position of the blocked polyphenol is substituted such that the 4-position of the functionalized polyphenol monomer is coupled to the 6-position of the blocked polyphenol.

35

The compounds prepared by the processes of this invention may be purified, e.g., compounds or combinations thereof can be substantially pure; for instance, purified to apparent homogeneity. Purity is  
5 a relative concept, and the numerous Examples demonstrate isolation of compounds or combinations thereof, as well as purification thereof, such that by methods exemplified a skilled artisan can obtain a substantially pure compound or combination thereof, or  
10 purify them to apparent homogeneity (e.g., purity by HPLC: observation of a single chromatographic peak). As defined herein, a substantially pure compound or combination of compounds is at least about 40% pure, e.g., at least about 50% pure, advantageously at least  
15 about 60% pure, e.g., at least about 70% pure, more advantageously at least about 75-80% pure, preferably, at least about 90% pure, more preferably greater than 90% pure, e.g., at least 90-95% pure, or even purer, such as greater than 95% pure, e.g., 95-98% pure.

20 Moreover, stereoisomers of the oligomers are encompassed within the scope of the invention. The stereochemistry of the substituents on a polyphenol monomeric unit of the oligomer may be described in  
25 terms of their relative stereochemistry, "alpha/beta" or "cis/trans", or in terms of absolute stereochemistry, "R/S". The term "alpha" ( $\alpha$ ) indicates that the substituent is oriented below the plane of the flavan ring, whereas, "beta" ( $\beta$ ) indicates that the  
30 substituent is oriented above the plane of the ring. The term "cis" indicates that two substituents are oriented on the same face of the ring, whereas "trans" indicates that two substituents are oriented on opposite faces of the ring. The terms R and S are used  
35 to denote the arrangement of the substituents about a stereogenic center, based on the ranking of the groups according to the atomic number of the atoms directly

position 6 and 8 of the adjacent monomeric unit; the stereochemical linkages between monomeric units is designated herein as (4 $\alpha$ →6) or (4 $\beta$ →6) or (4 $\alpha$ →8) or (4 $\beta$ →8) for linear oligomers. In addition to the

5 stereochemical differences in the interflavan bonding to carbon position 4, a bond to carbon position 2 may have alpha or beta stereochemistry, and a bond to carbon position 3 may have alpha or beta stereochemistry (e.g., (-)-epicatechin or

10 (+)-catechin). For linkages to a branched or junction monomeric unit, the stereochemical linkages are (6→4 $\alpha$ ) or (6→4 $\beta$ ) or (8→4 $\alpha$ ) or (8→4 $\beta$ ). When one polyphenol monomeric unit (e.g., C or EC) is linked to another polyphenol monomeric unit (e.g., EC or C), the

15 linkages are advantageously (4 $\alpha$ →6) or (4 $\alpha$ →8). Further regioisomers of the polyphenol oligomers are encompassed within the scope of this invention. One skilled in the art will appreciate that rotation of a number of bonds within the oligomer may be restricted

20 due to steric hindrance, particularly if the oligomer is substituted, such as with benzyl groups. Accordingly, all possible regioisomers and stereoisomers of the compounds of the invention are encompassed within the scope of the invention.

25

In yet another embodiment, the invention is directed to a process for the production of a desired regio- or stereoisomer of a polyphenol oligomer of the formula:

attached to that stereogenic center. For example, the flavanoid compound (+)-catechin, may be defined as (2R, trans)-2-(3',4'-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3,5,7-triol, or as

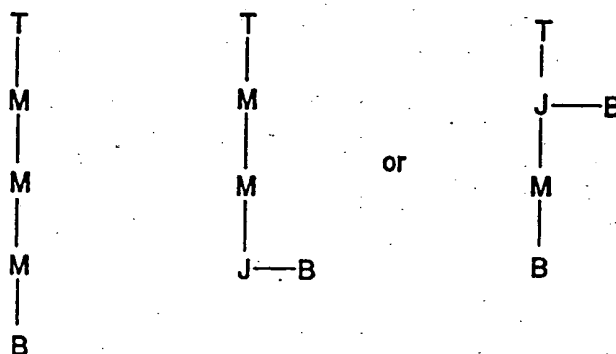
- 5 (2R,3S)-flavan-3,3',4',5,7-pentaol. Interflavan (polyphenol monomeric unit-polyphenol monomeric unit) bonding is often characterized using the relative terms  $\alpha/\beta$  or cis/trans;  $\alpha/\beta$  is used herein to designate the relative stereochemistry of the interflavan bonding.

10

Linear and branched polyphenol oligomers may be prepared by the process of this invention. Any polyphenol monomer may be used to prepare linear or branched oligomers containing monomeric units having

15 the same or of different flavanoid structures. The possible linkages between the monomeric units comprising the oligomers are distinguished by Top (T), Middle (M), Junction (J), and Bottom (B) linkages.

- 20 Representative examples for a linear pentamer and branched pentamer are shown below.



Linear pentamer

Branched pentamer

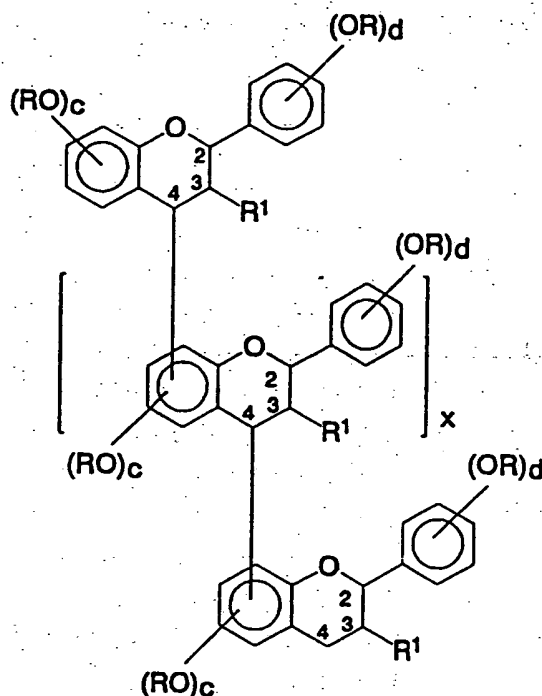
There are multiple stereochemical linkages, or bonding

25 orientation, between position 4 of a monomeric unit and

- 36 -

- C(O)styryl; wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy; and wherein each phenolic hydroxyl group of a polyphenol monomer is protected, comprising the steps of:
- (a) functionalizing the 4-position of a first polyphenol monomer having a selected stereochemistry;
  - (b) coupling said functionalized polyphenol monomer with a second polyphenol monomer having a selected stereochemistry to form a dimer having a selected regiochemistry;
  - (c) purifying said dimer;
  - (d) if x is equal to 1, functionalizing the 4-position of a third polyphenol monomer having a selected stereochemistry;
  - (e) coupling said functionalized third polyphenol monomer having a selected stereochemistry with said dimer to form a trimer having selected regiochemistry;
  - (f) purifying said trimer; and
  - (g) if x is greater than 1, sequentially adding functionalized polyphenol monomer to said trimer and successively higher oligomers by the steps recited above.

The invention is also directed to a process for producing a polyphenol oligomer of the formula:



wherein

x is an integer from 0 to 16;

c is independently an integer from 1 to 3;

5 d is independently an integer from 1 to 4;

R is independently C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl,

substituted benzyl, and a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, or, when c or d is 2 and are adjacent, diphenylmethylene or substituted

10 diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkoxy; and

15 R' is an -O-glycoside, an -O-substituted glycoside, -OC(O)aryl, -OC(O)-substituted aryl, -OC(O)-styryl, -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(-O)aryl, substituted -C(O)-aryl, -C(O)-styryl, substituted

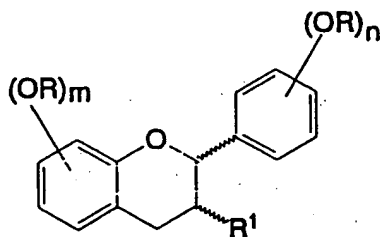


halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy; and

- R<sup>1</sup> is hydroxy, an -O-glycoside, an
- 5 -O-substituted glycoside, -OC(O)-aryl, -OC(O)-substituted aryl, -OC(O)-styryl, or -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, or
- 10 -C(O)-substituted styryl; wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and C<sub>3</sub>-C<sub>8</sub> cycloalkoxy;
- 15

which comprises:

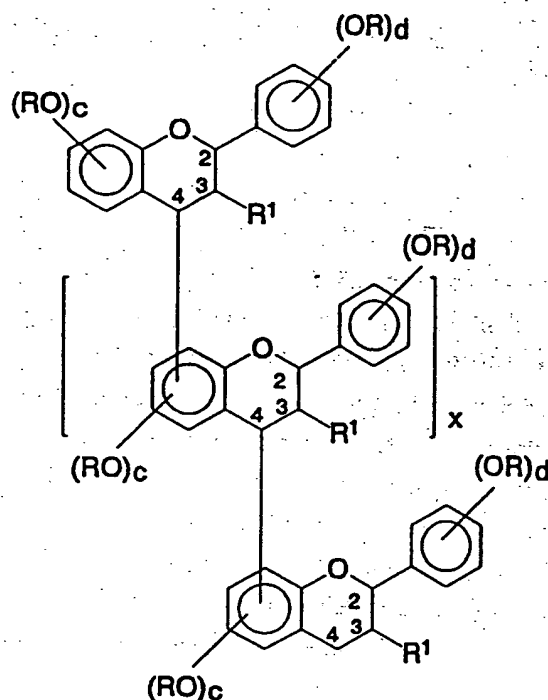
- (a) reacting a compound of the formula:



wherein

- 20 m is an integer from 1 to 3;  
n is an integer from 1 to 4; and  
R is C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, substituted benzyl, and a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, or, when c or d is 2 and are adjacent,
- 25 diphenylmethylenes or substituted diphenylmethylenes, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy;
- 30

R<sup>1</sup> is H or OH;



wherein

a bond to carbon position 2 has alpha or beta stereochemistry;

5 a bond to carbon position 3 has alpha or beta stereochemistry;

a bond to carbon position 4 has alpha or beta stereochemistry;

wherein:

10 c is independently an integer from 1 to 3;

d is independently an integer from 1 to 4;

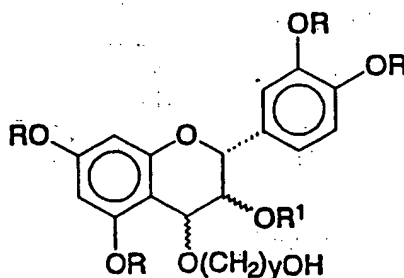
x is 0 to 16;

R is independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, substituted benzyl, and a silyl moiety

15 containing C<sub>1</sub>-C<sub>4</sub> alkyl or aryl substituents, or, when c or d is 2 and are adjacent, diphenylmethylenes or substituted diphenylmethylenes, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of

- 40 -

- (b) functionalizing the 4-position of the protected (+)-catechin or of the protected (-)-epicatechin to produce a functionalized protected (+)-catechin or a functionalized protected (-)-epicatechin having the formula:



wherein

- y is an integer from 2 to 6;  
R is a protecting group; and  
R' is hydrogen; and

- (c) coupling the protected (+)-catechin or the protected (-)-epicatechin with the functionalized protected (+)-catechin or the functionalized protected (-)-epicatechin to produce the polyphenol oligomer.

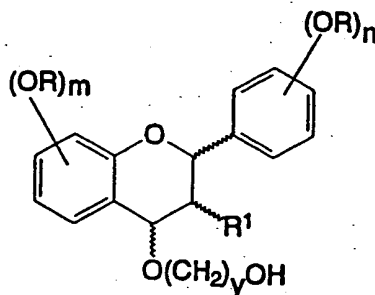
In another embodiment, the invention is directed to a process of preparing a procyanidin polyphenol oligomer comprised of n monomeric units of (+)-catechin or (-)-epicatechin, wherein n is an integer from 2 to 18, comprising:

- (a) protecting each phenolic hydroxyl group of a (+)-catechin or of a (-)-epicatechin with a suitable protecting group to produce a protected (+)-catechin or a protected (-)-epicatechin;

- (b) functionalizing the 4-position of the protected (+)-catechin or of the protected (-)-epicatechin to produce a functionalized protected (+)-catechin or a functionalized protected (-)-epicatechin having the formula:

(c) coupling the protected (+)-catechin or the protected (-)-epicatechin with the functionalized protected (+)-catechin or the functionalized protected (-)-epicatechin to produce the polyphenol oligomer.

with a compound of the formula:



wherein

m is an integer from 1 to 3;

5 n is an integer from 1 to 4;

y is an integer from 2 to 6; and

R is independently C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl,

substituted benzyl, and a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, or, when c or d is 2 and

10 are adjacent, diphenylmethane or substituted diphenylmethane, wherein said substituted benzyl or each substituted phenyl may contain substituents

selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy

15 C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy; and

R' is H or OH;

to form a protected polyphenol oligomer having protected phenolic hydroxyl groups; and

20 (b) deprotecting the phenolic hydroxyl groups of the protected polyphenol oligomer.

In a further embodiment, the invention is directed to a process for the production of a procyanidin polyphenol  
25 oligomer, which comprises:

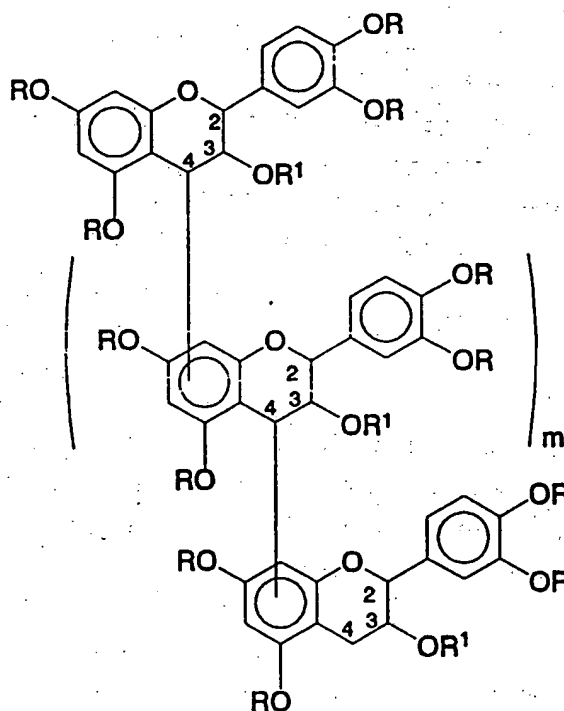
(a) protecting each phenolic hydroxyl group of a (+)-catechin or of a (-)-epicatechin with a protecting group to produce a protected (+)-catechin or a protected (-)-epicatechin;

(h) removing the protecting group from each phenolic hydroxyl group of the protected polyphenol oligomer to produce the polyphenol oligomer, wherein n equals 4 to 18.

5

Advantageously, each phenolic hydroxyl group is protected using a benzyl ether protecting group, and y is 2.

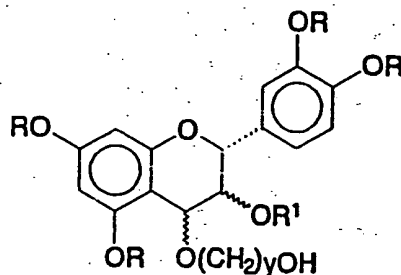
10 In a further embodiment, the invention is directed to a process for producing a procyanidin polyphenol oligomer of the formula:



wherein a bond to carbon position 2 has alpha or beta  
15 stereochemistry;

a bond to carbon position 3 has alpha or beta stereochemistry;

a bond to carbon position 4 has alpha or beta stereochemistry;



wherein

y is an integer from 2 to 6;

R is a protecting group; and

5 R' is hydrogen; and

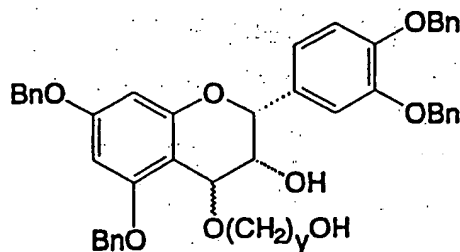
(c) coupling the protected (+)-catechin or the protected (-)-epicatechin with the functionalized protected (+)-catechin or the functionalized protected (-)-epicatechin to produce a protected polyphenol oligomer, wherein n equals 2;

(d) removing the protecting group from each phenolic hydroxyl group of the protected polyphenol oligomer to produce the polyphenol oligomer, wherein n equals 2,

(e) coupling the protected polyphenol oligomer, wherein n equals 2, with the functionalized protected (+)-catechin or the functionalized protected (-)-epicatechin to produce a protected polyphenol oligomer, wherein n equals 3,

(f) removing the protecting group from each phenolic hydroxyl group of the protected polyphenol oligomer to produce the polyphenol oligomer, wherein n equals 3,

(g) optionally repeating the process of coupling a protected polyphenol oligomer, where n equals 3 or more, with the functionalized protected (+)-catechin or the functionalized protected (-)-epicatechin to produce protected polyphenol oligomers, wherein n equals 4 to 18,



or a mixture thereof,  
wherein

y is an integer from 2 to 6;

5 to form a protected polyphenol oligomer having  
benzylated phenolic hydroxyl groups; and

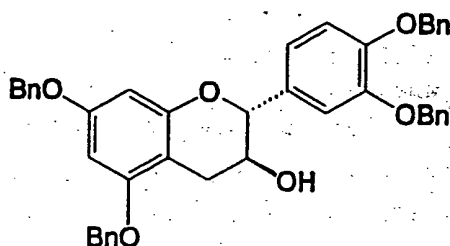
(b) deprotecting the benzylated phenolic  
hydroxyl groups of the protected polyphenol oligomer.

10 In a still further embodiment, the invention is  
directed to a process for producing a polyphenol  
oligomer of the formula:

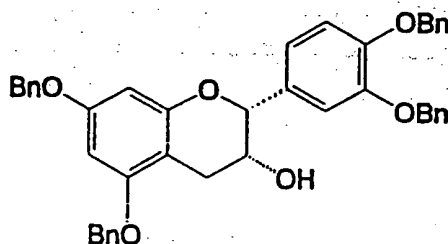
m is 0 to 16;  
 R is hydrogen; and  
 R' is hydrogen;

which comprises:

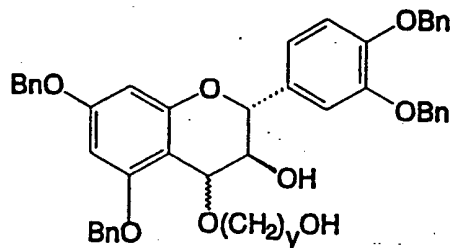
- 5 (a) reacting a compound selected from the group consisting of



and



- 10 or a mixture thereof, with a compound selected from the group consisting of

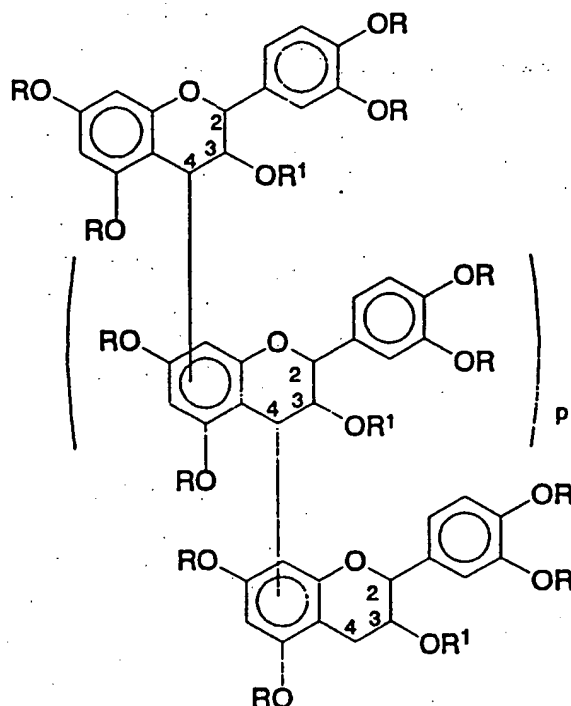


and



which comprises:

(a) reacting a compound of the formula:



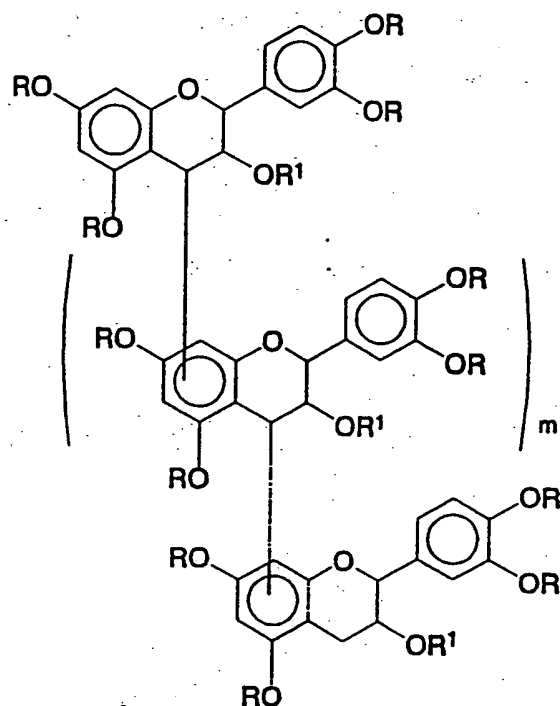
wherein a bond to carbon position 2 has alpha or beta stereochemistry;

a bond to carbon position 3 has alpha or beta stereochemistry;

a bond to carbon position 4 has alpha or beta stereochemistry;

10 p is 0 to 15;

R is independently C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, substituted benzyl, and a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, or, when c or d is 2 and are adjacent, diphenylmethylene or substituted diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkoxy; and



wherein a bond to carbon position 2 has alpha or beta stereochemistry;

a bond to carbon position 3 has alpha or beta stereochemistry;

a bond to carbon position 4 has alpha or beta stereochemistry;

m is 1 to 16;

R is hydrogen; and

R<sup>1</sup> is hydrogen;

10

Flavanoid compounds, (+)-catechin and (-)-epicatechin, are used herein to exemplify the types of polyphenol oligomers that may be prepared by the process of this invention. The linkages between the adjacent

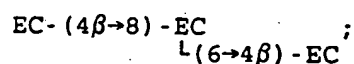
5 polyphenol monomeric units, (+)-catechin and (-)-epicatechin, abbreviated C and EC, respectively, are from position 4 to position 6 or position 4 to position 8; and this linkage between position 4 of a monomer and position 6 and 8 of the adjacent monomeric units is

10 designated herein as (4→6) or (4→8).

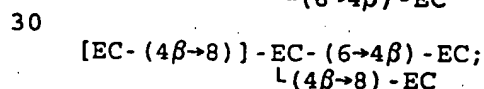
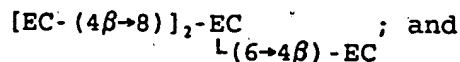
Examples of compounds within the scope of this invention include dimers, EC- (4β→8) -EC and EC-(4β→6) -EC, wherein EC- (4β→8) -EC is preferred; trimers [EC- (4β→8)]<sub>2</sub>-EC, [EC-(4β→8)]<sub>2</sub>-C and [EC-(4β→6)]<sub>2</sub>-EC, wherein

15 [EC-(4β→8)]<sub>2</sub>-EC is preferred; tetramers [EC-(4β→8)]<sub>3</sub>-EC, [EC-(4β→8)]<sub>3</sub>-C and [EC-(4β→8)]<sub>2</sub>-EC(4β→6)-C, wherein [EC-(4β→8)]<sub>3</sub>-EC is preferred; and pentamers [EC-(4β→8)]<sub>4</sub>-EC, [EC-(4β→8)]<sub>3</sub>-EC-(4β→6)-EC, [EC-(4β→8)]<sub>3</sub>-EC(4β→8)-C and

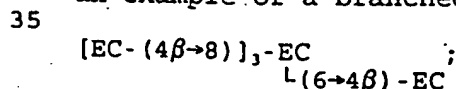
20 [EC-(4β→8)]<sub>3</sub>-EC-(4β→6)-C, wherein [EC-(4β→8)]<sub>4</sub>-EC is preferred. An example of a branched trimer is



25 examples of a branched tetramer include

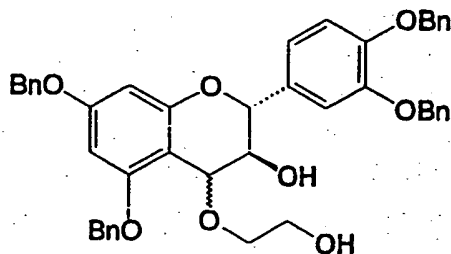


an example of a branched pentamer is

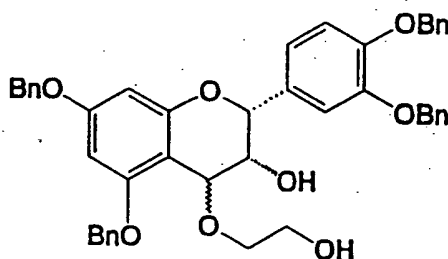


40 Additionally, compounds which elicit the activities cited above also include hexamers to dodecamers, examples of which are listed below:

$R_1$  is hydrogen, a glycoside, a substituted glycoside, -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, -C(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)aryl, -C(O)-substituted aryl, -C(O)-styryl, -C(O)-substituted styryl; wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy,  $C_3$ - $C_6$  cycloalkyl, and  $C_3$ - $C_6$  cycloalkoxy; with a compound selected from the group consisting of



and



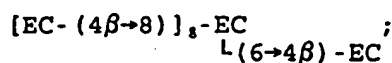
or a mixture thereof,  
 wherein

$$m = p + 1.$$

- 50 -

A decamer, wherein any combination of five monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g., [EC-(4 $\beta$ -8)]<sub>5</sub>-EC,

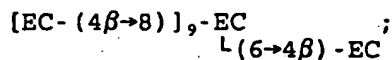
[EC-(4 $\beta$ -8)]<sub>4</sub>-EC-(4 $\beta$ -6)-EC, [EC-(4 $\beta$ -8)]<sub>3</sub>-EC-(4 $\beta$ -8)-C, and  
 5 [EC-(4 $\beta$ -8)]<sub>2</sub>-EC-(4 $\beta$ -6)-C; in a preferred embodiment, the decamer is [EC-(4 $\beta$ -8)]<sub>5</sub>-EC; an example of a branched decamer is



10

An undecamer, wherein any combination of six monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g., [EC-(4 $\beta$ -8)]<sub>10</sub>-EC,

15 [EC-(4 $\beta$ -8)]<sub>9</sub>-EC-(4 $\beta$ -6)-EC, [EC-(4 $\beta$ -8)]<sub>8</sub>-EC-(4 $\beta$ -8)-C, and [EC-(4 $\beta$ -8)]<sub>7</sub>-EC-(4 $\beta$ -6)-C; in a preferred embodiment, the undecamer is [EC-(4 $\beta$ -8)]<sub>10</sub>-EC; an example of a branched undecamer is



20

A dodecamer, wherein any combination of seven monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g., [EC-(4 $\beta$ -8)]<sub>11</sub>-EC,

25 [EC-(4 $\beta$ -8)]<sub>10</sub>-EC-(4 $\beta$ -6)-EC, [EC-(4 $\beta$ -8)]<sub>9</sub>-EC-(4 $\beta$ -8)-C, and [EC-(4 $\beta$ -8)]<sub>8</sub>-EC-(4 $\beta$ -6)-C; in a preferred embodiment, the dodecamer is [EC-(4 $\beta$ -8)]<sub>11</sub>-EC; an example of a branched

30 dodecamer is [EC-(4 $\beta$ -8)]<sub>10</sub>-EC  
 $|$   
 $L(6-4\beta)-EC$

It will be understood from the detailed description that the aforementioned list is exemplary and is  
 35 provided to illustrate the types of compounds that may be prepared by the processes of this invention and is not intended as an exhaustive list of the compounds encompassed by this invention.

A hexamer, wherein one monomer (C or EC) is linked to a pentamer compound listed above, e.g.,  $[EC-(4\beta\rightarrow 8)]_5-EC$ ,  $[EC-(4\beta\rightarrow 8)]_4-EC-(4\beta\rightarrow 6)-EC$ ,  $[EC-(4\beta\rightarrow 8)]_4-EC-(4\beta\rightarrow 8)-C$ , and  $[EC-(4\beta\rightarrow 8)]_4-EC-(4\beta\rightarrow 6)-C$ ; wherein  $[EC-(4\beta\rightarrow 8)]_5-EC$  is preferred; an example of a branched hexamer is

$$[EC-(4\beta\rightarrow 8)]_4-EC \quad ;$$

$$\quad \quad \quad L(6\rightarrow 4\beta)-EC$$

10 A heptamer, wherein any combination of two monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g.,  $[EC-(4\beta\rightarrow 8)]_6-EC$ ,  $[EC-(4\beta\rightarrow 8)]_5-EC-(4\beta\rightarrow 6)-EC$ ,  $[EC-(4\beta\rightarrow 8)]_5-EC-(4\beta\rightarrow 8)-C$ , and  $[EC-(4\beta\rightarrow 8)]_5-EC-(4\beta\rightarrow 6)-C$ ; in a preferred embodiment, the

15 heptamer is  $[EC-(4\beta\rightarrow 8)]_6-EC$ ; an example of a branched heptamer is

$$[EC-(4\beta\rightarrow 8)]_5-EC \quad ;$$

$$\quad \quad \quad L(6\rightarrow 4\beta)-EC$$

20 An octamer, wherein any combination of three monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g.,  $[EC-(4\beta\rightarrow 8)]_7-EC$ ,  $[EC-(4\beta\rightarrow 8)]_6-EC-(4\beta\rightarrow 6)-EC$ ,  $[EC-(4\beta\rightarrow 8)]_6-EC-(4\beta\rightarrow 8)-C$ , and

25  $[EC-(4\beta\rightarrow 8)]_6-EC-(4\beta\rightarrow 6)-C$ ; in a preferred embodiment, the octamer is  $[EC-(4\beta\rightarrow 8)]_7-EC$ ; an example of a branched octamer is

$$[EC-(4\beta\rightarrow 8)]_6-EC \quad ;$$

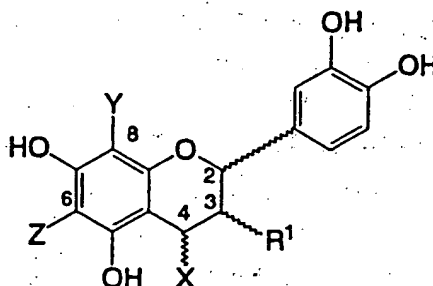
$$\quad \quad \quad L(6\rightarrow 4\beta)-EC$$

30 A nonamer, wherein any combination of four monomeric units (C and/or EC) are linked to a pentamer compound listed above, e.g.,  $[EC-(4\beta\rightarrow 8)]_8-EC$ ,

35  $[EC-(4\beta\rightarrow 8)]_7-EC-(4\beta\rightarrow 6)-EC$ ,  $[EC-(4\beta\rightarrow 8)]_7-EC-(4\beta\rightarrow 8)-C$ , and  $[EC-(4\beta\rightarrow 8)]_7-EC-(4\beta\rightarrow 6)-C$ ; in a preferred embodiment, the nonamer is  $[EC-(4\beta\rightarrow 8)]_8-EC$ ; an example of a branched nonamer is

$$[EC-(4\beta\rightarrow 8)]_7-EC \quad ;$$

40  $\quad \quad \quad L(6\rightarrow 4\beta)-EC$



wherein

n is an integer from 3 to 18, such that there is at least one terminal monomeric unit A, and a plurality of additional monomeric units;

R is 3-( $\alpha$ )-OH, 3-( $\beta$ )-OH, 3-( $\alpha$ )-O-sugar, or 3-( $\beta$ )-O-sugar;

bonding of adjacent monomers takes place between position 4 and positions 6 or 8;

a bond for an additional monomeric unit in position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of monomeric unit A, hydrogen, and a sugar, with the provisos that as to the at least one terminal monomeric unit, bonding of the additional monomeric unit thereto is at position 4 and optionally Y = Z = hydrogen;

the sugar is optionally substituted with a phenolic moiety, and

pharmaceutically acceptable salts, derivatives thereof, and oxidation products thereof; which process comprises the steps of:

(a) functionalizing the 4-position of a first polyphenol monomer;

(b) reacting said functionalized polyphenol monomer with a second polyphenol monomer to form a dimer;

(c) purifying said dimer;

The skilled artisan will recognize that the reaction sequence discussed above may be modified at the final stages to yield oligomers having  $x = 2-16$ , without undue experimentation. Higher oligomers, i.e.,  $x =$   
5 2-16, can be isolated by employing the dimer and/or trimer as the starting material for the coupling reaction, and the products derived therefrom may subsequently be used as starting material for coupling reactions to produce even higher oligomers.

10

Moreover, the skilled artisan will recognize that various reagents may be employed to practice the processes of this invention, without undue experimentation, and without departing from the spirit  
15 or scope thereof. Skilled artisans will be able to envision additional routes of synthesis, based on this disclosure and the knowledge in the art, without undue experimentation, e.g., based upon a careful retrosynthetic analysis of the polymeric compounds, as  
20 well as the monomers. For example, coupling of polyphenol monomers via an organometallic intermediate has been reported by K. Weinges et al. *Chem. Ber.* 103, 2344-2349 (1970). In addition, linear and branched polyphenol oligomers may be prepared by direct acid  
25 catalyzed coupling of monomeric polyphenol units, using conditions described by L. Y. Foo and R. W. Hemingway, *J. Chem. Soc., Chem. Commun.*, 85-86 (1984); J. J. Botha, et al., *J. Chem. Soc., Perkin I*, 1235-1245 (1981); J. J. Botha et al.; *J. Chem. Soc., Perkin I*,  
30 527-533 (1982), and H. Kolodziej, *Phytochemistry* 25, 1209-1215 (1986).

Accordingly, yet another embodiment of this invention is directed to a process for the production of a  
35 desired regio- or stereoisomer of a polymeric compound of the formula A<sub>n</sub>, wherein A is a monomer of the formula:



- 54 -

bonding of adjacent monomers takes place between position 4 and positions 6 or 8;

a bond for an additional monomeric unit in position 4 has alpha or beta stereochemistry;

5 X, Y and Z are selected from the group consisting of monomeric unit A, hydrogen, and a sugar, with the provisos that as to the at least one terminal monomeric unit, bonding of the additional monomeric unit thereto is at position 4 and optionally Y = Z =  
10 hydrogen;

the sugar is optionally substituted with a phenolic moiety, and pharmaceutically acceptable salts, derivatives thereof, and oxidation products thereof; which process comprises:

15 (a) protecting each phenolic hydroxyl group of a (+)-catechin or of a (-)-epicatechin with a protecting group to produce a protected (+)-catechin or a protected (-)-epicatechin;

(b) functionalizing the 4-position of the  
20 protected (+)-catechin or of the protected (-)-epicatechin or of a mixture thereof to produce a functionalized protected (+)catechin, a functionalized protected (-)-epicatechin or a functionalized protected mixture thereof;

25 (c) combining the protected (+)-catechin or the protected (-)-epicatechin with the functionalized protected (+)catechin or the functionalized protected (-)-epicatechin or mixtures thereof to produce a protected polyphenol oligomer;

30 (d) removing the protecting group from the phenolic hydroxyl groups of the polyphenol oligomer to produce an unprotected polyphenol oligomer; and

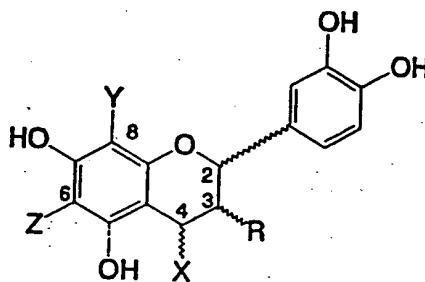
(e) optionally derivatizing the protected or  
35 unprotected polyphenol oligomer to produce a derivatized polyphenol oligomer.

- (d) functionalizing the 4-position of a third polyphenol monomer;
- (e) reacting said functionalized third polyphenol monomer with said dimer to form a trimer;
- 5 (f) purifying said trimer;
- (g) sequentially adding functionalized polyphenol monomer to said trimer and successively higher oligomers by the steps recited above; and
- (h) optionally derivatizing the protected or
- 10 unprotected polyphenol oligomer to produce a derivatized polyphenol oligomer.

Preferably, n is 5, the sugar is selected from the group consisting of glucose, galactose, xylose,

15 rhamnose and arabinose, and the phenolic moiety is selected from the group consisting of caffeic, cinnamic, coumaric, ferulic, gallic, hydroxybenzoic and sinapic acids.

- 20 The invention is further directed to a process for the production of a polymeric compound of the formula  $A_n$ , wherein A is a monomer of the formula:



wherein

- 25 n is an integer from 3 to 18, such that there is at least one terminal monomeric unit A, and a plurality of additional monomeric units;

R is 3-( $\alpha$ )-OH, 3-( $\beta$ )-OH, 3-( $\alpha$ )-O-sugar, or 3-( $\beta$ )-O-sugar;

sinapic acids. Also preferably, the compound is substantially pure, preferably purified to apparent homogeneity.

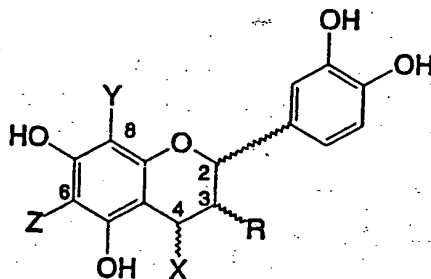
- 5 Derivatives of the compound wherein one or more of the phenolic hydroxyl groups is benzylated are also encompassed within the scope of the invention.

- Adjacent monomers may bind at position 4 by (4→6) or  
10 (4→8); and each of X, Y and Z is H, a sugar or an adjacent monomer, with the provisos that if X and Y are adjacent monomers, Z is H or sugar and if X and Z are adjacent monomers, Y is H or sugar, and that as to at least one of the two terminal monomers, bonding of the  
15 adjacent monomer is at position 4 and optionally, Y = Z = hydrogen.

- One or more of the monomeric units may be derivatized with a gallate or a  $\beta$ -D-glucose, including the  
20 3-position of a terminal monomeric unit.

- These processes may be used to prepare linear or branched oligomers containing repeating monomeric units of a single polyphenol monomer or of different  
25 polyphenol monomers. Moreover, given the phenolic character of the subject compounds, the skilled artisan can utilize various methods of phenolic coupling, selective protection/deprotection, organometallic additions, and photochemical reactions, e.g., in a  
30 convergent, linear or biomimetic approach, or combinations thereof, together with standard reactions known to those well-versed in the art of synthetic organic chemistry, as additional synthetic methods for preparing polyphenol oligomers. In this regard,  
35 reference is made to W. Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Ed., Cambridge University Press, 1986, and J. March, *Advanced Organic Chemistry*,

In still another embodiment, the invention is directed to a polymeric compound of the formula  $A_n$ , wherein A is a monomer of the formula:



5

wherein

n is an integer from 3 to 18, such that there is at least one terminal monomeric unit A, and a plurality of additional monomeric units;

10 R is 3-( $\alpha$ )-OH, 3-( $\beta$ )-OH, 3-( $\alpha$ )-O-sugar, or 3-( $\beta$ )-O-sugar;

bonding of adjacent monomers takes place between position 4 and positions 6 or 8;

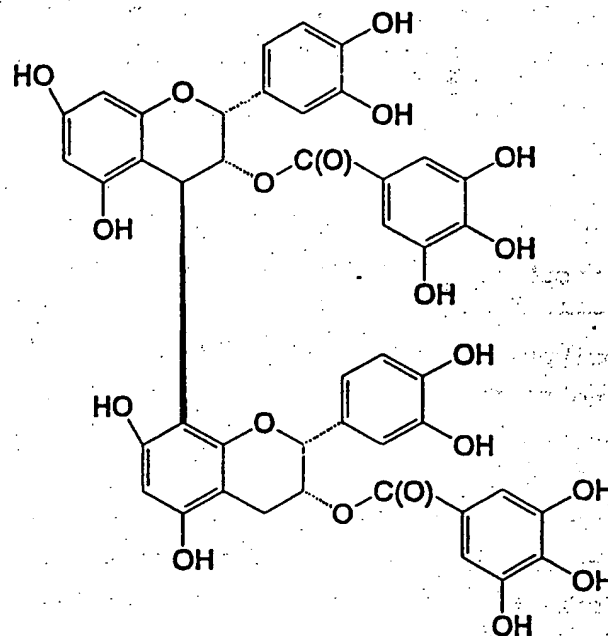
a bond for an additional monomeric unit in  
15 position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of monomeric unit A, hydrogen, and a sugar, with the provisos that as to the at least one terminal monomeric unit, bonding of the additional monomeric  
20 unit thereto is at position 4 and optionally Y = Z = hydrogen;

the sugar is optionally substituted with a phenolic moiety, and pharmaceutically acceptable salts, derivatives thereof, and oxidation products thereof.

25

Preferably, n is 5, the sugar is selected from the group consisting of glucose, galactose, xylose, rhamnose and arabinose, and the phenolic moiety is selected from the group consisting of caffeic,  
30 cinnamic, coumaric, ferulic, gallic, hydroxybenzoic and



and a pharmaceutically acceptable carrier or excipient,  
and to a method for treating a subject in need of  
treatment with an anticancer agent comprising  
5 administering to the subject an effective amount of the  
composition. The cancer includes breast cancer.

In still yet another embodiment, the invention is  
directed to a pharmaceutical composition comprising a  
10 compound of the formula:

3rd Ed., John Wiley & Sons, 1985, van Rensburg et al.,  
J. Chem. Soc. Chem. Commun. 24: 2705-2706 (Dec. 21,  
1996), Ballenegger et al., (Zyma SA) European Patent  
0096 007 B1, all of which are hereby incorporated  
5 herein by reference.

The process of this invention also provides a means for  
incorporation of a isotope label, e.g., deuterium and  
tritium, into polyphenol oligomers. For example, a  
10 polyphenol monomer or oligomer may be dissolved in D<sub>2</sub>O  
and CD<sub>3</sub>CN, and gently heated in order to initiate H-D  
exchange (this reaction can also be carried out using  
T<sub>2</sub>O and CH<sub>3</sub>CN in order to incorporate a tritium into the  
molecule). Alternatively, deuterium or tritium may be  
15 incorporated using the methods of M. C. Pierre et al.,  
*Tetrahedron Letters* 38, (32), 5639-5642 (1997) or  
E. Keihlmann et al., *Can. J. Chem.*, 26, 2431-2439  
(1988). The incorporation of a deuterium or tritium  
atom in the polyphenol oligomer facilitates the  
20 determination of how polyphenol compounds may be  
metabolized following ingestion.

The polyphenol oligomers, and derivatives thereof,  
prepared by the process of this invention have the same  
25 uses, and are formulated, purified and administered in  
the same manner as described in U.S. Patent Application  
No. 08/831,245 filed April 2, 1997.

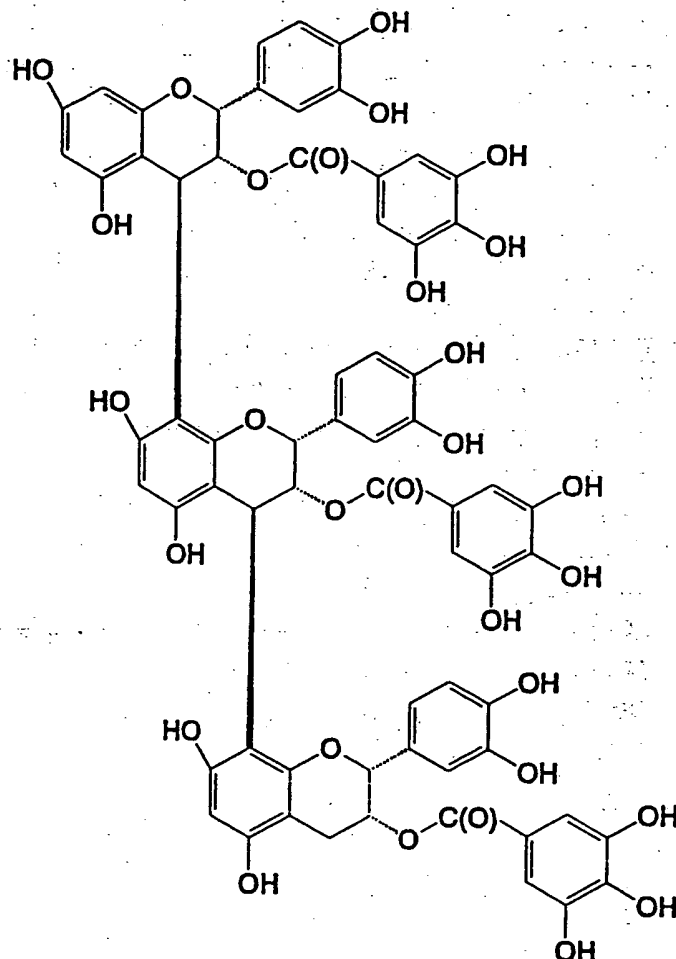
This invention is also directed to a pharmaceutical  
composition comprising a compound of the formula:

trimer substantially increased the antineoplastic activity of these oligomers. Thus, the gallation of oligomers produces compounds that are useful for the uses described in U.S. application Serial No.

- 5 08/831,245, filed April 2, 1997. Further, the following table lists exemplary examples of gallated oligomers useful for the uses described in U.S. Patent Application No. 08/831,245, filed April 2, 1997.

- 10 Table: Gallated Procyanidin Oligomers  
EC-3-O-galloyl-(4 $\beta$ →8)-EC-3-O-gallate  
C-3-O-galloyl-(4 $\alpha$ →8)-EC-3-O-gallate  
C-3-O-galloyl-(4 $\alpha$ →8)-C  
EC-(4 $\beta$ →8)-EC-3-O-gallate  
15 C-(4 $\alpha$ →8)-EC-3-O-gallate  
EC-3-O-galloyl-(4 $\beta$ →8)-C  
EC (4 $\beta$ →8)-EC-3-O- $\beta$ -D-glucose-4,6-bisgallate  
[EC-3-O-galloyl-(4 $\beta$ →8)],-EC-3-O-gallate  
[EC-3-O-galloyl-(4 $\beta$ →8)],-EC-3-O-gallate  
20 [EC-(4 $\beta$ →8)]<sub>4</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>5</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>6</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>7</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>8</sub>-EC-3-O-gallate  
25 [EC-(4 $\beta$ →8)]<sub>9</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>10</sub>-EC-3-O-gallate  
[EC-(4 $\beta$ →8)]<sub>11</sub>-EC-3-O-gallate

- The Examples which follow are intended as an  
30 illustration of certain preferred embodiments of the invention, and no limitation of the invention is implied. The skilled artisan will recognize many variations in these examples to cover a wide range of formulas and processing to rationally adjust the  
35 compounds of the invention for a variety of applications without departing from the spirit or scope of the invention.



and a pharmaceutically acceptable carrier or excipient,  
 and to a method for treating a subject in need of  
 treatment with an anticancer agent comprising  
 5 administering to the subject an effective amount of the  
 composition. The cancer includes breast cancer.

Examples 8 and 10 describe the preparation of a dimer  
 bisgallate and trimer trisgallate, respectively. Their  
 10 *in vitro* assessment (Example 25 against several human  
 breast cancer cell lines showed activity equivalent to  
 the pentamer. These results were surprising, since  
 gallation of previously inactive procyanidin dimer and



5.17 (narrow ABq, 2 H), 5.03 (s, 2 H), 4.99 (s, 2 H), 4.63 (d, 1 H, J=8.5 Hz), 4.00 (m, 1 H), 3.11, 2.65 (ABq, 2 H, J=16.5 Hz, both parts d with J=5.5 and 9 Hz, resp.), 1.59 (d, 1 H, J=3.5 Hz); IR (film) 3440 (br), 1618, 1593, 1513, 1499, 1144, 1116, 733, 696  $\text{cm}^{-1}$ ; MS  $m/z$  650 ( $M^+$ , 0.5%), 319, 181, 91.

Alternatively, the tetra-O-benzyl (+)-catechin may be prepared using the method described by H. Kawamoto et al, *Mokazai Gakkaishi*, 37, (5) 488-493 (1991), using potassium carbonate and benzyl bromide in DMF. Partial racemization of catechin, at both the 2- and 3-positions, was observed by M.-C. Pierre et al., *Tetrahedron Letters*, 38, (32) 5639-5642 (1997).

15

## EXAMPLE 2

Preparation of (2R)-5,7,3',4'  
Tetrakis(benzyloxy)flavan-3-one

20 Freshly prepared Dess-Martin periodinane (39.0 g, 92 mmol, prepared by the method of D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.* 113, 7277-7287 (1991) and R. E. Ireland and L. Liu, *J. Org. Chem.* 58, 2899 (1993)), was added at room temperature, all at once, to  
25 a stirred solution of the tetra-O-benzylcatechin according to Example 1 (54.4 g, 83.8 mmol) in methylene chloride (420 mL). Within 1.5 h, approx. 30 mL of water-saturated methylene chloride was added dropwise to the reaction mixture to form a turbid amber-colored  
30 solution. (S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 59, 7549-7552 (1994)) Twenty minutes thereafter, the reaction mixture was diluted with a saturated solution of sodium carbonate ( $\text{NaHCO}_3$ , 500 mL) and a 10% aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  (200 mL). The  
35 phases were separated and the aqueous phase extracted with 50 mL of methylene chloride. The combined organic phases were filtered over silica gel (24 x 9 cm, chloroform/ethyl acetate 9: 1). The eluate was

In the following examples, (+)-catechin and (-)-epicatechin are exemplary polyphenol monomers used to demonstrate the processes of the present invention and no limitation of the invention is implied. The (-)-epicatechin as used herein, may be obtained from commercial sources, or protected epicatechin may be prepared from protected (+)-catechin (Example 3).

## EXAMPLE 1

10 Preparation of (2R,3S, trans)-  
5,7,3',4'-Tetra-O-benzylcatechin

A solution of (+)-catechin (65.8 g, 226.7 mmol, anhydrous), dissolved in anhydrous dimethylformamide (DMF, 720 mL), was added dropwise, at room temperature over a period of 80 min, to a stirred suspension of sodium hydride, 60% in oil, (39 g, 975 mmol, 4.3 eq.) in DMF (180 mL). (S. Miura, et al., *Radioisotopes*, 32, 225-230 (1983)) After stirring for 50 min, the flask was placed in a -10°C NaCl/ice bath. Benzyl bromide (121 mL, 1.02 mol, 4.5 eq.) was added dropwise within 80 min. and the brown reaction mixture warmed to room temperature, with stirring, overnight. The resulting reaction mixture was evaporated and the resulting candy-like solid was dissolved, with heating and stirring, in two portions of solvent each consisting of 200 mL of chloroform (CHCl<sub>3</sub>) and 100 mL of water. The phases were separated, the aqueous phase extracted with CHCl<sub>3</sub> (20 mL), and the combined organic phases washed with water (100 mL), dried over magnesium sulfate (MgSO<sub>4</sub>) and evaporated. The residue was purified by chromatography on silica gel (42 x 10 cm; ethyl acetate/chloroform/hexane 1:12:7) to provide, after evaporation and drying in vacuo, 85 g crude product, which was recrystallized from trichloroethylene (1.3 L) to provide 35.1 g (24%) of an off-white powder. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.47-7.25 (m, 20 H), 7.03 (s, 1 H), 6.95 (s, 2 H), 6.27, 6.21 (ABq, 2 H, J=2 Hz), 5.18 (s, 2 H),

ethanol (EtOH), (2:3), and allowed to crystallize at room temperature, then in the refrigerator. The product was isolated by suction filtration, washed with 2 x 50 mL of cold (-20°C) EtOAc/EtOH (1:3), and dried in vacuo first at room temperature, then at 80°C to obtain 35.4 g (70%) of a light yellow solid. The evaporated mother liquor was filtered over silica gel, SiO<sub>2</sub>, (14 x 6.5 cm, CHCl<sub>3</sub>, then CHCl<sub>3</sub>/EtOAc 12:1), the eluate concentrated to 40 mL, and the residue diluted with 60 mL of ethanol, to obtain an additional 5.5 g (11%) of the O-benzylepicatechin as a yellowish solid: mp 129.5-130°C (from EtOAc/EtOH); [ $\alpha$ ]<sub>D</sub> -27.7°, [ $\alpha$ ]<sub>M</sub> -33.4° (EtOAc, c 21.6 g/L); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.48-7.25 (m, 20 H), 7.14 (s, 1 H), 7.00, 6.97 (ABq, 2 H, J=8.5 Hz, A part d with J=1.5 Hz), 6.27 (s, 2 H), 5.19 (s, 2 H), 5.18 (s, 2 H), 5.02 (s, 2 H), 5.01 (s, 2 H), 4.91 (s, 1 H), 4.21 (br s, 1 H), 3.00, 2.92 (ABq, 2 H, J=17.5 Hz, both parts d with J=1.5 and 4 Hz, resp.), 1.66 (d, 1 H, J=5.5 Hz); Anal. Calcd. for C<sub>43</sub>H<sub>38</sub>O<sub>6</sub>: C, 79.36; H, 5.89. Found: C, 79.12; H, 5.99.

## EXAMPLE 4

## Preparation of (2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-4-(2-hydroxyethoxy)epicatechin

Ethylene glycol (6.4 mL, 115 mmol, 5.8 eq.) was added, at room temperature, with stirring, to a solution of the tetra-O-benzylepicatechin according to Example 3 (12.75 g, 19.6 mmol) in 130 mL of anhydrous methylene chloride, followed by addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 8.9 g, 39.2 mmol, 2.0 eq.), at one time, with vigorous stirring. (J.A. Steenkamp, et al., *Tetrahedron Letters*, 26, (25) 3045-3048 (1985)). After approximately 2 hours, 4-dimethylaminopyridine (DMAP, 4.8 g, 39.2 mmol) was added to the reaction mixture, resulting in the formation of a dark green precipitate. After stirring for an additional 5 minutes, 100 g of

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evaporated and dried in vacuo to obtain 50.1 g (92%) of the ketone, which was purified by recrystallization from chloroform/ether: mp 144-144.5°C;  $[\alpha]_D +38.5^\circ$ ,  $[\alpha]_{44} +48.7^\circ$  (chloroform, c 20.8 g/L);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  7.45-7.26 (m, 20 H), 6.96 (s, 1 H), 6.88, 6.86 (ABq, 2 H,  $J=8$  Hz, B part d with  $J=1.5$  Hz), 6.35 (narrow ABq, 2 H), 5.24 (s, 1 H), 5.14 (s, 2 H), 5.10 (narrow ABq, 2 H), 5.02 (s, 2 H), 5.01 (s, 2 H), 3.61, 3.45 (ABq, 2 H,  $J=21.5$  Hz).

10

## EXAMPLE 3

## Preparation of 5,7,3',4'-Tetra-O-benzylepicatechin

A 1 M solution of lithium tri-sec-butylborohydride in tetrahydrofuran, herein after THF, (100 mL, L-Selectride®, sold by the Aldrich Chemical Co, Inc., Milwaukee, WI) was added, under an argon atmosphere, to a stirred, 0°C solution of anhydrous lithium bromide, LiBr, (34.9 g, 402 mmol) in 100 mL anhydrous THF. The resulting mixture was cooled to -78°C, using an acetone/ $\text{CO}_2$  bath, followed by dropwise addition of a solution of the flavanone according to Example 2 (50.1 g, 77.2 mmol) in 400 mL of anhydrous THF, over a period of 50 min. Stirring was continued at -78°C for 135 min. The cooling bath was removed and 360 mL of 2.5 M aqueous sodium hydroxide (NaOH) was added to the reaction mixture. The reaction flask was placed in a room temperature water bath and a mixture of 35% aqueous  $\text{H}_2\text{O}_2$  (90 mL) and ethanol (270 mL) was added over a period of 130 min. Stirring was continued overnight. Chloroform (700 mL) was added to dissolve the crystallized product, the phases were separated, the aqueous phase was extracted with  $\text{CHCl}_3$  (50 mL), the combined organic phases were dried over  $\text{MgSO}_4$ , evaporated and dried in vacuo to provide 56.6 g of crude product. This material was dissolved in 600 mL of a boiling mixture of ethyl acetate (EtOAc) and

35

NaHCO<sub>3</sub> and 100 mL of water (resulting pH: 8). The resulting mixture was extracted with methylene chloride (2 x 20 mL). The combined organic layers were washed with 50 mL of water, dried over MgSO<sub>4</sub>, evaporated and  
5 dried in vacuo. The resulting glass deposited a pink solid upon dissolution in methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>) and standing at room temperature. The solid was filtered off, washed with 3 x 15 mL of CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1), and dried in vacuo to obtain 6.1 g of recovered  
10 tetra-O-benzylepicatechin. From the evaporated mother liquor, the oligomers were isolated by column chromatography on silica gel (45 x 5.2 cm). Elution with CH<sub>2</sub>Cl<sub>2</sub>/hexane/EtOAc (13:13:1) provided an additional 4.9 g of recovered tetra-O-  
15 benzylepicatechin, followed by 2.17 g of crude O-benzyl dimer. Elution of the dimer was completed using methylene chloride/hexane/EtOAc (10:10:1). Elution of 0.98 g of crude O-benzyl trimer and 0.59 g of higher oligomers was obtained using methylene  
20 chloride/hexane/EtOAc (8:8:1 to 6:6:1). The dimer and the trimer were further purified by preparative HPLC on a silica gel column, using ethyl acetate/hexane or ethyl acetate/isooctane as eluent. Peak detection was performed with a UV detector at 265 or 280 nm. Trimer:  
25 MS (MALDI-TOF, DHBA matrix) *m/z* (M + H<sup>+</sup>) 1949.4; calcd. for C<sub>129</sub>H<sub>110</sub>O<sub>18</sub>: 1947.8; (M + Na<sup>+</sup>) 1971.2; calcd. for C<sub>129</sub>H<sub>110</sub>O<sub>18</sub>Na: 1969.8; (M + K<sup>+</sup>) 1988.3; calcd. for C<sub>129</sub>H<sub>110</sub>O<sub>18</sub>K: 1985.7.

30

## EXAMPLE 6

## Preparation of Epicatechin Dimer

To a solution of the O-benzyl-dimer according to Example 5 (22.3 mg, 17.2 μmol) in 0.5 mL of ethyl  
35 acetate was added sequentially, 2 mL of methanol and 7.2 mg of 10% Pd/C. The mixture was stirred under 1 bar of H<sub>2</sub> for 3 hours and filtered over cotton. The

- 65 -

silica gel was added, and the mixture was concentrated under reduced pressure. The residue was placed on top of a silica gel column (11 x 6.5 cm) which was eluted with EtOAc/hexane (1:1), and the eluate was concentrated under reduced pressure. The resulting crude material was re-purified by chromatography on silica gel (39 x 10 cm, EtOAc/hexane (1:2), followed by EtOAc/hexane (2:3)) to provide, after evaporation and drying, in vacuo, 7.3 g (52%) of the benzyl-4-(2-hydroxyethoxy) epicatechin, as a foam or solid, which was recrystallized from acetonitrile: mp 120-121°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48-7.26 (m, 20 H), 7.14 (d, J=1.5 Hz), 7.02, 6.97 (ABq, 2 H, J=8 Hz, A part d with J=1.5 Hz), 6.29, 6.26 (ABq, 2 H, J=2 Hz), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.10 (s, 1 H), 5.08, 5.02 (ABq, 2 H, partially concealed), 5.00 (s, 2 H), 4.59 (d, 1 H, J=2.5 Hz), 3.95 (br, 1 H), 3.82-3.74 (m, 1 H), 3.72-3.57 (m, 3 H), 2.17 (br, 1 H), 1.64 (d, 1 H, J=5.5 Hz); IR (film) 3450 (br), 1616, 1592, 1512, 1152, 1114, 735, 697 cm<sup>-1</sup>. Anal. Calcd. for C<sub>25</sub>H<sub>32</sub>O<sub>8</sub>: C, 76.04; H, 5.96. Found: C, 76.57; H, 6.02.

## EXAMPLE 5

## Preparation of O-Benzylepicatechin (4B-8) Oligomers

To a cold (0°C), stirred solution of the benzyl-4-(2-hydroxyethoxy) epicatechin according to Example 4 (3.28 g, 4.6 mmol) and the tetra-O-benzyl-epicatechin according to Example 3 (12.0 g, 18.4 mmol, 4 eq.) in anhydrous THF (40 mL) and anhydrous methylene chloride (50 mL), was added dropwise, in 10 min, titanium tetrachloride (4.6 mL of 1 M TiCl<sub>4</sub> in methylene chloride). (H. Kawamoto et al, *Mokazai Gakkaishi*, 37, (5) 448-493 (1991)). The resulting amber-colored solution was stirred in the ice bath for 5 min, then at room temperature for 90 min. The reaction was terminated by addition of 30 mL of saturated aqueous

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(1:19). Concentration of the eluate and drying in vacuo yielded 36.0 mg (97%) of the O-benzyl dimer bisgallate as a colorless film:  $[\alpha]_D -53.3^\circ$ ,  $[\alpha]_{446} -65.6^\circ$  ( $\text{CH}_2\text{Cl}_2$ , c 15.7 g/L); IR (film) 1720, 1591, 1498, 1428, 1196, 1112, 736, 696  $\text{cm}^{-1}$ ; MS (MALDI-TOF, DHBA matrix)  $m/z$  ( $M + K^+$ ) 2181.8; calcd. for  $\text{C}_{142}\text{H}_{118}\text{O}_{20}\text{K}$ : 2181.8; ( $M + \text{Na}^+$ ) 2165.9; calcd. for  $\text{C}_{142}\text{H}_{118}\text{O}_{20}\text{Na}$ : 2165.8.

10

## EXAMPLE 8

## Preparation of Epicatechin Dimer Bisgallate

To a solution of the O-benzyl dimer bisgallate according to Example 7 (33.8 mg, 15.8  $\mu\text{mol}$ ) in 4 mL of THF was added sequentially 4 mL of methanol, 0.2 mL of water, and 42 mg of 20%  $\text{Pd}(\text{OH})_2/\text{C}$ . The mixture was stirred under 1 bar of  $\text{H}_2$  for 75 minutes and filtered over cotton. The filtration residue was washed with 2.2 mL of methanol/ $\text{H}_2\text{O}$  (10:1) and the combined filtrate was concentrated under reduced pressure to provide 14.2 mg of yellowish, amorphous crude product. A 7.2 mg aliquot was purified by preparative HPLC (silica gel, ethyl acetate/hexane; detection at 280 nm) to yield 5.0 mg (71%) of the polyphenol dimer bisgallate as a turbid pinkish glass from which small amounts of ethanol and acetic acid could not be removed:  $^1\text{H}$  NMR (acetone- $d_6/\text{D}_2\text{O}$  3:1 v/v, TMS, most signals broad)  $\delta$  7.08 (s, 2 H, sharp), 7.1-6.7 (m, 7 H), 6.66 (d, 1 H, sharp,  $J=8$  Hz), 6.17 (s, 1 H), 5.94 (s, 2 H), 5.70 (s, 1 H), 5.49 (s, 1 H), 5.44 (s, 1 H), 4.9 (very br, 1 H), 4.80 (s, 1 H), 3.08, 2.88 (ABq, 2 H,  $J=17$  Hz, A part d,  $J=4$  Hz); MS (MALDI-TOF, DHBA matrix)  $m/z$  ( $M + \text{Na}^+$ ) 904.9; calcd. for  $\text{C}_{44}\text{H}_{34}\text{O}_{20}\text{Na}$ : 905.2.

filtration residue was washed with methanol and the combined filtrates were evaporated. An NMR spectrum of the crude product indicated the presence of benzylated material. The procedure was therefore repeated, with  
5 the amount of catalyst increased to 17.5 mg and the time extended to 3.7 h. The crude polyphenol dimer (9.6 mg) was purified by preparative HPLC ( $C_{18}$  reverse phase column water/methanol (85:15) with addition of 0.5% acetic acid, detection at 265 nm) to provide 4.5  
10 mg (45%) of polyphenol dimer as an amorphous film.  $^1H$  NMR (300 MHz, acetone- $d_6$ /D $_2$ O 3:1 (v/v), TMS)  $\delta$  7.19 (br, 1 H), 7.01 (overlapping s + br, 2 H), 6.86-6.65 (m, 4 H), 6.03 (br, 3 H), 5.10 (br, 1 H), 5.00 (br, 1 H), 4.69 (br, 1 H), 3.97 (s, 1 H), 2.92, 2.76 (br ABq, 2 H,  
15 J = 17 Hz); MS (MALDI-TOF, DHBA matrix)  $m/z$  (M +  $K^+$ ) 616.8; calcd. for  $C_{30}H_{26}O_{12}K$ : 617.1; (M +  $Na^+$ ) 600.8; calcd. for  $C_{30}H_{26}O_{12}Na$ : 601.1.

## EXAMPLE 7

## 20 Preparation of O-Benzylepicatechin Dimer Bisgallate

To a solution of tri-O-benzyl gallic acid (38 mg, 87  $\mu$ mol, 5 eq.), DMF (1  $\mu$ L) in methylene chloride (0.6 mL), was added oxalyl chloride (15  $\mu$ L, 172  $\mu$ mol, 10  
25 eq.). The resulting reaction mixture was stirred at room temperature for approximately 1 hour, evaporated and dried in vacuo to provide tri-O-benzyl galloyl chloride. A solution of the O-benzyl-dimer according to Example 5 (22.5 mg, 17.3  $\mu$ mol) in anhydrous pyridine  
30 (0.5 mL) was added to the crude galloyl chloride at room temperature, and the resulting mixture was stirred for 44.5 h. After addition of 20  $\mu$ L of water, stirring was continued for 2.5 h, followed by addition of 10 mL of 5% HCl. The resulting mixture was extracted with  
35 methylene chloride (3 x 5 mL), the combined organic phases were dried over  $MgSO_4$ , evaporated and purified by filtration over silica gel using with EtOAc/ $CHCl_3$ .



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MHz,  $\text{CDCl}_3$ , TMS)  $\delta$  7.5-7.25 (m, 20 H), 7.23 (d, 1 H,  $J$  = 1.5 Hz), 7.03, 6.98 (ABq, 2 H,  $J$  = 8.5 Hz, A part d with  $J$  = 1 Hz), 6.25 (s, 1 H), 5.22 (s, 2 H), 5.19 (s, 2 H), 5.11 (s, 2 H), 5.02, 4.96 (ABq, 2 H,  $J$  = 9 Hz),  
5 4.98 (s, 1 H), 4.27 (br s, 1 H), 3.04, 2.90 (ABq, 2 H,  $J$  = 17.5 Hz, both parts d with  $J$  = 1.5 and 4 Hz, resp.), 1.58 (d, 1 H,  $J$  = 4.5 Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.86, 154.79, 151.65, 149.09, 148.73, 137.31, 137.15, 136.77, 136.72, 130.82, 128.67, 128.65, 128.58,  
10 128.56, 128.09, 127.98, 127.87, 127.50, 127.31, 127.25, 127.13, 118.91, 115.17, 113.07, 102.85, 93.07, 78.62, 71.35, 71.20, 70.31, 65.92, 28.00; IR (mineral oil suspension) 3571, 1606, 1581, 1518, 1184, 1129, 771, 732, 694  $\text{cm}^{-1}$ ; MS  $m/z$  399/397 (1/1%), 332 (1%), 181  
15 (8%), 91 (100%). Anal. calcd. for  $\text{C}_{43}\text{H}_{37}\text{O}_6\text{Br}$ : C, 70.78; H, 5.11. Found: C, 70.47; H, 5.10.

Method B: To 563 mg (771  $\mu\text{mol}$ ) of 5,7,3',4-tetra-8-bromocatechin, prepared by the method described in  
20 Example 1, in 5 mL of  $\text{CH}_2\text{Cl}_2$  was added at room temperature all at once 425 mg (1.00 mmol) of Dess-Martin periodinane. Water-saturated  $\text{CH}_2\text{Cl}_2$  was added dropwise within 40 min to produce a slight turbidity. After another 20 min, 20 mL each of saturated  $\text{NaHCO}_3$ ,  
25 solution and a 10% aqueous solution of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  were added. The phases were separated and the aqueous phase extracted with 3 x 15 mL of ether. The combined organic phases were concentrated and the residue filtered over silica gel (20 x 2.5 cm, ether/hexane  
30 1:1). The eluate was evaporated and dried in vacuo to obtain 522 mg (93%) of the ketone as a colorless foam:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$  7.47-7.25 (m, 20 H), 7.04 (d, 1 H,  $J$  = 1 Hz), 6.85, 6.81 (ABq, 2 H,  $J$  = 8.5 Hz, B part d with = 8.5 Hz), 3.52, 3.48 (ABq, 2 H,  $J$  = 21.5 Hz);  $^{13}\text{C}$  NMR  
35 ( $\text{CDCl}_3$ ,  $\delta$  203.99, 155.55, 155.40, 150.68, 148.98, 137.06, 136.90, 136.28, 136.04, 128.64, 128.62, 128.46, 128.41, 128.22, 128.05, 127.78, 127.76, 127.35, 127.17, 127.13,

## EXAMPLE 9

## Preparation of O-Benzylepicatechin Trimer Trisgallate

Using the procedure described in Example 7, O-benzyl  
5 trimer trisgallate was obtained from the O-benzyl  
trimer according to Example 5 in 78% yield after  
purification by HPLC (conditions: silica gel, ethyl  
acetate/hexane, 280 nm); <sup>1</sup>H NMR: extremely complex; IR  
(film) 3031, 1719, 1594, 1498, 1428, 1116, 735, 696  
10 cm<sup>-1</sup>.

## EXAMPLE 10

## Preparation of Epicatechin Trimer Trisgallate

15 Using the procedure described in Example 8, polyphenol  
trimer trisgallate was obtained from the O-benzyl  
trimer trisgallate according to Example 9 in 60% yield  
after purification by HPLC. (C<sub>18</sub> reverse phase gradient  
of 15-25% B in A, where A is 0.5 vol.% acetic acid  
20 (AcOH) in water and B is 0.5% AcOH in ethanol; 280 nm);  
<sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O/acetone-d<sub>6</sub> 1:3 (v/v)) δ 7.10 (s,  
2 H), 7.1-6.88 (m, 7 H), 6.82-6.70 (m, 3 H), 6.68-6.60.

## EXAMPLE 11

25 Preparation of  
8-Bromo-5,7,3',4'-tetra-O-benzylepicatechin

Method A: To a solution of 116 mg (178 μmol) of  
tetra-O-benzylepicatechin in 4 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>,  
30 was added with ice cooling and stirring 32 mg (180  
μmol) of N-bromosuccinimide (NBS). Stirring at 0°C was  
continued for 100 min, the solution was concentrated,  
and the residue was purified by chromatography on  
silica gel (15 x 1.8 cm) with CHCl<sub>3</sub>/EtOAc (25:1).  
35 Crystallization from CHCl<sub>3</sub>/ethanol gave 110 mg (85%) of  
a colorless, cotton-like solid. Mp 137.5°C; [α]<sub>D</sub> -  
50.4°, [α]<sub>346</sub> -60.7° (c 17.3 g/L, EtOAc); <sup>1</sup>H NMR (300

5,7,3',4'-tetra-O-methyl-4-(2-hydroxyethoxy)epicatechin according to Example 5 to yield a mixture of tetramers having the fourth epicatechin moiety attached to the 6-positions predominantly of the bottom and center epicatechin moieties, as well as higher oligomers. The

desired intermediate,  
O-methyl-8-bromo-EC-(4 $\beta$ →8)-EC-(6→4 $\beta$ )-EC  
L(4 $\beta$ →8)-EC

is isolated by preparative HPLC as in Example 11. The  
10 purified intermediate is de-brominated by treatment of  
its THF solution at low temperature, preferably at  
-78°C, with an excess of an alkylolithium, preferably n-  
or tert-butyllithium, and protonation of the resulting  
solution or suspension of the lithiated protected  
15 branched tetramer by addition of a weak proton acid,  
such as water or an alcohol.

#### EXAMPLE 13

20 Preparation of O-Benzylepicatechin Tetramer  
Tetragallate

Using the procedure described in Example 7, the  
O-benzylepicatechin tetramer tetragallate is obtained  
from the O-benzylepicatechin tetramer according to  
25 Example 12.

#### EXAMPLE 14

Preparation of Epicatechin Tetramer Tetragallate

30 Using the procedure described in Example 8, the  
epicatechin tetramer tetragallate is obtained from the  
O-benzylepicatechin tetramer tetragallate according to  
Example 13.

127.08, 126.99, 118.86, 114.59, 112.43, 103.54, 93.96, 93.87, 82.91, 71.25, 71.04, 70.98, 70.38, 33.30; IR (film) 1734, 1605, 1513, 1099, 737 696  $\text{cm}^{-1}$ .

- 5 To 598 mg (822  $\mu\text{mol}$ ) of the above crude ketone in 8.2 mL of anhydrous THF was added dropwise within 10 min 1.23 mL of a 1 M solution of lithium tri-sec-butylborohydride (L-Selectride®). After stirring at -78°C for 3h, starting material was still detectable in  
10 the reaction mixture by thin layer chromatography, "TLC," ( $\text{SiO}_2$ , EtOAc/hexane 1:3), and another 1.23 mL of the reducing agent was added. Stirring was continued for another 4 h while the temperature was gradually allowed to rise to -4°C. Aqueous NaOH (2.5 M, 6 mL) and  
15 4 mL of 35% aqueous  $\text{H}_2\text{O}_2$  were added with continued cooling; the resulting exotherm raised the bath temperature to +12°C. Stirring in the water bath was continued overnight, then the mixture was partially evaporated, and 20 mL ether and 10 mL of EtOAc were  
20 added. The phases were separated, and the aqueous phase was extracted with 50 mL of EtOAc. The combined organic phases evaporated, and the residue was purified by chromatography on silica gel (23 x 2.5 cm) with EtOAc/hexane 1:3 to obtain 327 mg (55%) of the product  
25 as a light-yellow foam.

#### EXAMPLE 12

##### Preparation of O-Methylepicatechin Tetramer

- 30 The O-methylepicatechin trimer (prepared according to Examples 1 through 5, except that in Example 1, methyl iodide or dimethyl sulfate and potassium carbonate in acetone is used to prepare the protected monomer, tetra-O-methylcatechin) is brominated in position 8 of  
35 the top epicatechin moiety using either of the procedures of Example 11. The resulting bromo derivative is reacted with

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recrystallized *N*-bromosuccinimide (NBS). The reaction mixture was stirred at 0°C for 45 min and at room temperature for 17 h. A solution of 200 mg of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 5 mL of water was added. After brief stirring, the phases were separated, the aqueous phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ , and the combined organic phases were dried over  $\text{MgSO}_4$  and evaporated. Chromatography on silica gel (30 x 2.6 cm) with  $\text{EtOAc}/\text{CHCl}_3/\text{hexane}$  1:12:7 (to remove a trace byproduct) then 3:12:7, was followed by evaporation and drying in vacuo to give 362 mg (87%) of the dibromide as a colorless foam:  $[\alpha]_{\text{D}}^{25} -58.2^\circ$ , ( $\text{EtOAc}$ ,  $c$  13.5  $\text{g/L}^{-1}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.64 (d, 2 H,  $J = 7$  Hz), 7.52-7.26 (m, 18 H), 7.17 (s, 1 H), 7.03, 6.97 (s, 2 H), 5.20 (s, 2 H), 5.17 (s, 2 H), 5.03 (s, 2 H), 5.01, 4.97 (ABq, 2 H,  $J = 11$  Hz), 4.99 (s, 1 H), 4.19 (narrow m, 1 H), 3.04, 2.87 (ABq,  $J = 17.5$  Hz, both parts d with  $J = 1.5$  and 3.5 Hz, resp.), 1.55 (d, 1 H,  $J = 3.5$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  154.43, 152.57, 151.09, 149.03, 148.82, 137.10, 136.94, 136.50, 136.37, 130.13, 128.52, 128.50, 128.48, 128.47, 128.43, 128.35, 128.32, 128.16, 127.82, 127.81, 127.36, 127.20, 118.81, 115.06, 112.91, 112.30, 105.23, 103.25, 78.80, 74.61, 74.55, 71.24, 71.14, 65.33, 28.75; IR (film) 1734, 1606, 1513, 1369, 1266, 1184, 1113, 1083, 735, 697  $\text{cm}^{-1}$ . Anal. Calcd, for  $\text{C}_{43}\text{H}_{36}\text{O}_6\text{Br}_2$ : C, 63.88; H, 4.49. Found: C, 64.17; H, 4.45.

## EXAMPLE 17

## 5,7,3',4'-Tetra-O-benzyl-6,8,6'-tribromoepicatechin

30

To a solution of 1.72 g (2.65 mmol) of 5,7,3',4-tetra-O-benzylepicatechin in 26 mL of anhydrous  $\text{CH}_2\text{Cl}_2$ , was added with ice cooling all at once 1.89 g (10.6 mmol) of recrystallized *N*-bromosuccinimide. The reaction mixture was stirred at 0°C for 1 h and at room temperature for 20 h. A solution of 3 g of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 25 mL of water was added. Partial phase separation

35

## EXAMPLE 15

## 3,5,7,3',4-Penta-O-benzyl-8-bromoepicatechin

To 53 mg (1.3 mmol) of sodium hydride (60% suspension  
5 in mineral oil) was added with stirring at 0°C under N<sub>2</sub>,  
738 mg (1.01 mmol) of 5,7,3',4-tetra-O-benzyl-8-  
bromoepicatechin in 2 mL of anhydrous DMF. After 10  
min, 0.18 mL (1.5 mmol) of neat benzyl bromide was  
added. The mixture was stirred at 0°C for 145 min and  
10 at room temperature for 5.5 h, then 0.1 mL of water was  
added. Chromatography on SiO<sub>2</sub> (27 x 2.6 cm) with  
EtOAc/hexane 1:4 and drying in vacuo (room temperature,  
then 80°C) yielded 650 mg (78%) of the product as a  
yellowish glass:  $[\alpha]_D -52.6^\circ$ ,  $[\alpha]_{46} -63.4^\circ$  (EtOAc, c  
15 17.9 gL<sup>-1</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.50-7.14 (m, 23 H), 6.99  
(m, 2 H), 6.94, 6.91 (ABq, 2 H, J = 8.5 Hz, A part d  
with J = 1.5 Hz), 6.23 (s, 1 H), 5.19 (s, 2 H), 5.11  
(s, 5 H), 4.97 (s, 2 H), 4.38, 4.30 (ABq, 2 H, J = 12.5  
Hz), 3.97 (narrow m, 1 H), 2.95, 2.80 (ABq, 2 H, J = 17  
20 Hz, both parts d with J = 3.5 and 4.5 Hz, resp.); <sup>13</sup>C  
NMR (CDCl<sub>3</sub>)  $\delta$  156.44, 154.62, 151.94, 148.65, 137.92,  
137.41, 137.26, 136.75, 136.71, 131.68, 128.56, 128.53,  
128.38, 128.12, 128.00, 127.85, 127.70, 127.62, 127.43,  
127.33, 127.25, 127.19, 127.02, 119.15, 114.74, 113.29,  
25 103.40, 93.11, 92.76, 78.06, 72.13, 71.32, 71.26,  
71.21, 70.83, 70.22, 24.73; IR (film) 1605, 1580, 1513,  
1454, 1346, 1265, 1125, 1095, 735, 697; IR (film) 1605,  
1580, 1513, 1454, 1346, 1265, 1125, 1095, 735, 697 cm<sup>-1</sup>.  
Anal. Calcd. for C<sub>30</sub>H<sub>43</sub>O<sub>6</sub>Br: C, 73.26; H, 5.29. Found C,  
30 72.81; H, 5.12.

## EXAMPLE 16

## 5,7,3',4-Tetra-O-benzyl-6,8-dibromoepicatechin

35 To a solution of 334 mg (914  $\mu$ mol) of 5,7,3',4-tetra-O-  
benzylepicatechin in 10 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub> was added  
with ice cooling all at once 192 mg (1.08 mmol) of

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N-bromosuccinimide. The reaction mixture was stirred in the thawing cold bath, which after 65 min had reached 0 °C. A solution of 50 mg of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 1 mL of water was added, the cold bath was removed, and  
5 the mixture was stirred for 15 min at room temperature. The phases were separated, and the organic phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{MgSO}_4$ , concentrated, and purified via chromatography on silica gel (33 x 1.6 cm) with  
10 EtOAc/hexane 1:1 (Note 1). After starting material and mixed fractions containing comparable concentrations of both components had been eluted, fractions consisting mostly of the desired product were collected. These fractions were further purified by preparative HPLC  
15 (Whatman Partisil 10,500 x 9.4 mm, EtOAc/hexane 1:1, 5 mL/min, detection at 280 nm). The major peak with  $t_r$  14.4 min was isolated:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.49-7.25 (m, 20 H), 7.23 (d, 1 H,  $J = 1$  Hz), 7.05, 6.98 (ABq, 2 H,  $J = 8$  Hz, A part d with  $J = 1.5$  Hz), 6.28 (s, 1 H), 5.23  
20 (s, 3 H), 5.19 (s, 2 H), 5.12 (s, 2 H), 5.05, 4.99 (ABq, 2 H,  $J = 11.5$  Hz), 4.63 (d, 1 H,  $J = 3$  Hz), 4.03 (br, 1 H), 3.83-3.76 (m, 1 H), 3.74-3.56 (m, 3 H), 2.11 (br, 1 H), 1.57 (br, 1 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.30, 156.61, 152.17, 149.09, 148.73, 137.18, 137.07, 136.39,  
25 136.02, 130.04, 128.68, 128.61, 128.49, 128.46, 128.33, 127.98, 127.79, 127.60, 127.45, 127.23, 126.93, 118.95, 115.16, 113.24, 103.36, 92.78, 75.05, 71.30, 71.21, 71.09, 70.83, 70.70, 70.23, 67.90, 61.89; IR (film) 3380 (br), 1603, 1577, 1514, 1187, 1130, 1111, 733, 696  
30  $\text{cm}^{-1}$ .

Method B: To 44.1 mg (43.3  $\mu\text{mol}$ ) of the bis(TBDMS) ether of Example 19, dissolved in 0.4 mL of anhydrous THF, was added 0.19 mL of a tetrabutylammonium fluoride  
35 solution (1 M in THF). The mixture was stirred in a closed flask for 4 hours, then evaporated, and the residue was purified via chromatography on silica gel.

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occurred only after addition of 30 mL of brine, 230 mL of water, and 130 mL of  $\text{CH}_2\text{Cl}_2$ . Residual emulsion was set aside, the aqueous phase was extracted with 100 mL of  $\text{CH}_2\text{Cl}_2$ , and this organic phase and 200 mL of water were shaken in a separatory funnel with the emulsion. Again phase separation was incomplete, and the remaining emulsion was extracted a last time with 100 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried over  $\text{MgSO}_4$  and concentrated. Chromatography on silica gel (17 x 4.5 cm) with  $\text{EtOAc}/\text{CHCl}_3/\text{hexane}$  1:12:7, then 1:15:4 was followed by evaporation and drying in vacuo to give 2.01 g (85%) of the tribromide as a light-tan solid. The analytical sample was obtained by crystallization from  $\text{CHCl}_3/\text{EtOH}$ : mp 154-156°C;  $[\alpha]_D^{25}$  112°,  $[\alpha]_{460}^{25}$  -135° ( $\text{EtOAc}$ , c 9.7  $\text{g/L}^{-1}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ,  $\delta$  7.66 (d, 2 H, 6.5 Hz), 7.52 (d, 2 H,  $J = 6.5$  Hz), 7.48-7.26 (m, 17 H), 7.14 (s, 1 H), 5.28 (s, 1 H), 5.23 (s, 2 H), 5.17 (s, 2 H), 5.06 (s, 2 H), 5.02 (s, 2 H), 4.44 (narrow m, 1 H), 3.10, 2.95 (ABq,  $J = 17$  Hz, A part br, B part d with  $J = 4$  Hz), 1.35 (d, 1 H,  $J = 4$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ,  $\delta$  154.54, 152.53, 151.09, 149.15, 148.32, 136.49, 136.44, 136.40, 136.31, 128.72, 128.54, 128.52, 128.48, 128.42, 128.36, 128.33, 128.16, 128.02, 127.89, 127.41, 127.27, 118.84, 114.58, 112.30, 111.42, 105.38, 103.14, 78.61, 74.62, 74.58, 71.46, 70.96, 62.66, 28.99; IR (film) 1499, 1385, 1367, 1266, 1182, 1109, 1083, 734, 695  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{43}\text{H}_{33}\text{O}_6\text{Br}_3$ : C, 58.20; H, 3.98. Found: C, 58.52; H, 3.80.

30

## EXAMPLE 18

(2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-8-bromo-4-(2-hydroxyethoxy)epicatechin

Method A: To a solution of 202 mg (284  $\mu\text{mol}$ ) of (2R,3S,4S)-5,7,3',4'-tetra-O-benzyl-4-(2-hydroxyethoxy)epicatechin in 4 mL of  $\text{CH}_2\text{Cl}_2$ , was added at -78 °C all at once 51 mg (286  $\mu\text{mol}$ ) of recrystallized



## EXAMPLE 20

(2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-8-bromo-3-O-(tert-butyldimethylsilyl)-4-[2-(tert-butyldimethylsilyl)oxy]ethoxy]epicatechin

5

To a solution of 2.61 g (2.78 mmol) of (2R,3S,4S)-5,7,3',4'-tetra-O-benzyl-3-O-(tert-butyldimethylsilyl)-4-[2-[(tert-butyldimethylsilyl)oxy]ethoxy]epicatechin, in 35 mL of  $\text{CH}_2\text{Cl}_2$ , was added at  $-78^\circ\text{C}$ , all at once, 500 mg (2.81 mmol) of recrystallized N-bromosuccinimide. The reaction mixture was stirred in the thawing cold bath, which after 6 h had reached  $+20^\circ\text{C}$ . A solution of 0.5 g of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 10 mL of water was added, the cold bath was removed, and the mixture was stirred for 15 10 min at room temperature. The phases were separated, and the organic phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were concentrated and filtered over silica gel with EtOAc/hexane 1:4. Evaporation and drying in vacuo resulted in 2.72 g 20 (96%) of the product as a colorless glass:  $[\alpha]_D - 25.8^\circ$ ,  $[\alpha]_{446} - 31.6^\circ$  (EtOAc, c 20.2  $\text{g/L}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.51-7.25 (m, 20 H), 7.22 (s, 1 H), 6.98, 6.94 (ABq, 2 H,  $J = 8$  Hz, A part br), 6.22 (s, 1 H), 5.30 (s, 1 H), 5.19 (s, 2 H), 5.17 (s, 2 H), 5.11 (s, 2 H), 5.06, 25 4.98 (ABq, 2 H,  $J = 12$  Hz), 4.54 (d, 1 H,  $J = 3$  Hz), 3.94 (br d, 1 H,  $J = 2.5$  Hz), 3.73-3.60 (m, 4 H), 0.88 (s, 9 H), 0.60 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H), -0.24 (s, 3 H), -0.56 (s, 3 H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  158.04, 156.11, 152.88, 148.92, 148.05, 137.42, 137.31, 136.62, 30 136.59, 132.24, 128.59, 128.52, 128.41, 128.37, 128.01, 127.85, 127.69, 127.63, 127.45, 127.31, 127.19, 126.99, 119.46, 115.41, 113.76, 103.75, 92.61, 91.79, 75.78, 71.60, 71.05, 71.03, 70.61, 70.47, 70.14, 69.30, 62.65, 25.94, 25.47, 18.39, 17.90, -5.10, -5.19, -5.50; IR (film) 2952, 2928, 285, 1605, 1578, 1257, 1186, 1135, 35 1114, 835, 777, 735, 696  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{37}\text{H}_{49}\text{O}_8\text{BrSi}_2$ : C, 67.24; H, 6.83. Found: C, 67.35; H, 6.57.

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(15 x 1.8 cm) with EtOAc/CHCl<sub>3</sub>/hexane 1:12:7 (to remove a forerun), then 1:19:0. The eluate was evaporated and dried in vacuo to yield 32.7 mg (96%) of the product as a colorless film.

5

## EXAMPLE 19

(2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-3-O-(tert-butyldimethylsilyl)-4-[2-[(tert-butyldimethylsilyl)oxy]ethoxy]epicatechin

10

To solution of 2.18 g (3.07 mmol) of (2R,3S,4S)-5,7,3'-4'-tetra-O-benzyl-4-(2-hydroxyethoxy)epicatechin and 0.63 g (9.2 mmol) of imidazole in 5 mL of anhydrous DMF was added at room temperature, all at once, 1.30 g (8.6 mmol, 2.8 eq.) of tert-butyldimethylsilyl chloride. The mixture was stirred at room temperature in a stoppered flask for 24 h and then directly filtered over silica gel (33 x 3.7 cm) with EtOAc/hexane 1:6 to give, after evaporation and drying in vacuo, 2.63 g (91%) of the product as a colorless glass:  $[\alpha]_D +3.9^\circ$ ,  $[\alpha]_{546} +4.7^\circ$  (EtOAc, c 9.0 gL<sup>-1</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.51-7.28 (m, 20 H), 7.12 (d, 1 H, J = 1 Hz), 6.98, 6.93 (ABq, 2 H, J = 8 Hz, A part d with J = 1 Hz), 6.24, 6.22 (ABq, 2 H, J = 2 Hz), 5.19, 5.14 (ABq, 2 H, partially concealed), 5.17 (s, 2 H), 5.09-4.96 (2 overlapping ABq, 4 H), 4.50 (d, 1 H, J = 3 Hz), 3.89 (br d, 1 H, J = 2.5 Hz), 3.69 (m, 4 H), 0.88 (s, 9 H), 0.67 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H), -0.21 (s, 3 H), -0.48 (s, 3 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  160.12, 159.39, 156.63, 148.88, 148.30, 137.37, 137.02, 136.83, 132.65, 128.53, 128.49, 128.42, 128.38, 127.94, 127.82, 127.75, 127.67, 127.62, 127.51, 127.33, 127.26, 120.14, 115.28, 114.29, 102.23, 94.28, 93.17, 75.22, 71.5, 71.40, 70.63, 70.32, 70.11, 69.98, 69.61, 62.71, 25.95, 25.59, 18.38, 17.90, -5.10, -5.18, -5.25, -5.40; IR (film) 2952, 2928, 2855, 1616, 1593, 1257, 1153, 1136, 1108, 835, 777, 735, 696 cm<sup>-1</sup>. Anal. Calcd, for C<sub>57</sub>H<sub>70</sub>O<sub>8</sub>Si<sub>2</sub>: C, 72.88; H, 7.51. Found: C, 73.35; H, 7.04.

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## EXAMPLE 22

(2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-6,8,6'-tribromo-4-(2-hydroxyethoxy)epicatechin

5 To 73.4 mg (62.4  $\mu$ mol) of the bis(TBDMS) ether in 0.4 mL of anhydrous THF was added 0.25 mL of tetrabutylammonium fluoride solution (1 M in THF). The mixture was stirred in a closed flask for 2.5 h, then evaporated, and the residue was purified via  
10 chromatography on silica gel (15 x 1 cm) with EtOAc/hexane 1:2 (to remove a forerun), then 1:1. The evaporated eluate was further purified by preparative thin layer chromatography (SiO<sub>2</sub>, 200 x 200 x 2 mm, EtOAc/hexane 1:1) to yield 44.8 mg (76%) of the product  
15 as a colorless film:  $[\alpha]_D -81.6^\circ$ ,  $[\alpha]_{446} -98.3^\circ$  (EtOAc, c 10.1 gL<sup>-1</sup>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.65 (d, 2 H. J = 6.5 Hz), 7.54 (d, 2 H. J = 6.5 Hz), 7.48-7.24 (m, 17 H), 7.13 (s, 1 H), 5.57 (s, 1 H), 5.24, 5.08 (ABq, 2 H. J = 11 Hz), 5.22, 5.18 (ABq, 2 H. J = 11.5 Hz), 5.13 (s, 2  
20 H), 5.06 (s, 2 H), 4.45 (d, 1 H, J = HZ), 4.25 (br, 1 H), 3.84-3.76 (m, 1 H), 3.72-3.58 (m, 3 H), 2.11 (br, 1 H), 1.48 (br, 1 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 156.24, 154.70, 151.52, 149.24, 148.39, 136.50, 136.38, 136.18, 128.60, 128.58, 128.52, 128.51, 128.49, 128.44, 128.09, 128.06,  
25 128.03, 127.94, 127.46, 127.27, 118.92, 115.03, 112.99, 111.33, 105.40, 103.41, 76.04, 75.08, 74.66, 71.50, 71.08, 71.03, 70.96, 64.12, 61.95; IR (film) 3500 (br), 1580, 1500, 1365, 1262, 1193, 1121, 1097, 736, 696 cm<sup>-1</sup>.

30

## EXAMPLE 23

[5,7,3,4'-Tetra-O-benzyl-8-bromo-3-O-(tert-butyldimethylsilyl)epicatechin]-(4,8)-(5,7,3',4'-tetra-O-benzylepicatechin)

35

To a solution of 97.3 mg (95.6  $\mu$ mol) of (2R,3S,4S)-5,7,3',4'-tetra-O-benzyl-8-bromo-3-O-(tert-butyldimethylsilyl)-4-[2-[(tert-

## EXAMPLE 21

(2R,3S,4S)-5,7,3',4'-Tetra-O-benzyl-6,8,6'-tribromo-3-O-(tert-butyldimethylsilyl)-4-[2-  
[(tert-butyldimethylsilyl)oxy]ethoxy]epicatechin

- 5 To a solution of 96.0 mg (94.3  $\mu\text{mol}$ ) of (2R,3S,4S)-5,7,3',4'-tetra-O-benzyl-8-bromo-3-O-(tert-butyldimethylsilyl)-4-[2-[(tert-butyldimethylsilyl)oxy]ethoxy]epicatechin in 1.2 mL of
- 10  $\text{CH}_2\text{Cl}_2$ , was added at room temperature, all at once (65 mg, 365  $\mu\text{mol}$ , 3.87 eq.) of recrystallized N-bromosuccinimide. The reaction mixture was held at room temperature for 20.5 h, then a solution of 0.5 g of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 5 mL of water was added, and the
- 15 mixture was stirred for 10 min at room temperature. The phases were separated, and the organic phase was extracted with 2 x 5 mL of  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were concentrated and filtered over silica gel (34 x 1.1 cm) with EtOAc/hexane 1:12. Evaporation and
- 20 drying in vacuo resulted in 90.3 mg (81%) of the product as a colorless glass  $[\alpha]_{\text{D}}^{25} -74.1^\circ$  (EtOAc, c 9.0  $\text{g/L}^{-1}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.64 (d, 2H, J = 7 Hz), 7.60 (d, 2H, J = 7 Hz), 7.49-7.28 (m, 17H), 7.13 (s, 1 H), 5.62 (s, 1 H), 5.24, 4.97 (ABq, 2 H, J = 11 Hz), 5.16 (s, 4
- 25 H), 5.09 (s, 2 H), 4.53, 4.43 (ABq, 2 H, J = 2.5 Hz, B past br), 3.09-3.81 (m, 1 H), 3.80-3.71 (m, 3 H), 0.84 (s, 9 H), 0.65 (s, 9 H), -0.02 (s, 3 H), -0.16 (s, 3 H), -0.57 (s, 3 H) (one Si-CH<sub>3</sub> signal presumably coinciding with TMS);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  156.15, 154.11,
- 30 153.92, 148.72, 148.65, 136.90, 136.69, 136.58, 136.38, 129.61, 128.52, 128.50, 128.45, 128.43, 128.32, 128.16, 127.94, 127.91, 127.64, 127.44, 127.33, 119.23, 115.83, 113.33, 110.94, 104.76, 103.01, 75.85, 75.64, 74.56, 71.75, 71.50, 70.89, 70.79, 64.27, 62.55, 25.97, 25.58,
- 35 18.44, 17.73, -5.24, -5.30, -5.80; IR (film) 2927, 2856, 1499, 1360, 1259, 1106, 836  $\text{cm}^{-1}$ .

## EXAMPLE 24

(5,7,3',4'-Tetra-O-benzyl-8-bromoe catechin)-  
(4,8)-(5,7,3',4'-tetra-O-benzylepicatechin)

5 Method A: To a solution of 78.6 mg (99.5  $\mu\text{mol}$ ) of  
(2R,3S,4S)-5,7,3',4'-tetra-O-benzyl-8-bromo-4-(2-  
hydroxyethoxy)epicatechin and 324 mg (498  $\mu\text{mol}$ , 5 eq.)  
of 5,7,3',4'-tetra-O-benzylepicatechin in 0.85 mL of  
anhydrous THF and 1.1 mL of anhydrous  $\text{CH}_2\text{Cl}_2$ , was added  
10 with stirring and exclusion of moisture at 0 °C 0.10 mL  
(0.10 mmol) of a 1 M solution of  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$ . After  
3.5 h at room temperature, 3 mL of an saturated  $\text{NaHCO}_3$ ,  
aqueous solution and 10 mL of  $\text{CH}_2\text{Cl}_2$ , were added, the  
phases were separated, and the organic phase was dried  
15 over  $\text{MgSO}_4$  and evaporated. The residue was filtered  
over  $\text{SiO}_2$ , eluting sequentially with  $\text{EtOAc}/\text{CHCl}_3/\text{hexane}$   
1:12:7 (to remove most of the unreacted tetra-O-  
benzylepicatechin), then 1:19:0. The desired product  
was isolated from the evaporated crude product by  
20 preparative HPLC (Whatman Partisil 10, 500 x 9.4 mm,  
 $\text{EtOAc}/\text{hexane}$  1:4, 5 mL/min, detection at 280 nm,  $t_R$  27.5  
mm) to obtain 36.3 mg (26%) of a glass.

Method B: To a solution of 60.4 mg (46.5  $\mu\text{mol}$ ) of O-  
25 benzylated epicatechin 4,8-dimer in 0.9 mL of anhydrous  
 $\text{CH}_2\text{Cl}_2$ , was added at -78 °C all at once 8.3 mg (47  $\mu\text{mol}$ )  
of recrystallized N-bromosuccinimide. The reaction  
mixture was stirred and allowed to thaw to 0 °C during  
1.5 h, then stirred at 0 °C for 40 min. Thin Layer  
30 chromatography of the mixture ( $\text{SiO}_2$ ,  $\text{EtOAc}/\text{toluene}$  1:9)  
showed that some material with the same mobility as the  
starting material ( $R_f$  0.49) was present besides a  
product ( $R_f$  0.43). The mixture was re-cooled to -40 °C,  
and an additional 2.2 mg (12  $\mu\text{mol}$ ) of NBS was added.  
35 After the mixture had thawed to 0 °C within 70 min.,  
the thin layer chromatogram of the mixture remained  
unchanged, and the reaction was terminated by briefly

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- butyldimethylsilyl)oxy]ethoxy]epicatechin and 311 mg (478  $\mu\text{mol}$ , 5 eq.) of 5,7,3',4'-tetra-O-benzylepicatechin in 0.85 mL of anhydrous THF and 1.1 mL of anhydrous  $\text{CH}_2\text{Cl}_2$  was added with stirring and exclusion of moisture at  $0^\circ\text{C}$ , 0.10 mL (0.10 mmol) of a 1 M solution of  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$ . After 140 min at room temperature, 5 mL of saturated aq.  $\text{NaHCO}_3$  and 10 mL of  $\text{CH}_2\text{Cl}_2$  were added, the phases were separated, and the aqueous phase was extracted with 2 x 10 mL of  $\text{CH}_2\text{Cl}_2$ .
- The combined organic phases were dried over  $\text{MgSO}_4$  and evaporated, and the residue was filtered over silica gel with EtOAc/toluene 1:19. Evaporation and drying in vacuo gave 239 mg of a foam the components of which could be separated only by preparative HPLC (Whatman Partisil 10, 500 X 9.4 mm, EtOAc/toluene 1:24, 5 mL/min, detection at 290 nm). From 234 mg of this mixture, 34.8 mg of the desired product was obtained at  $t_r$  10.3 min. Remaining minor impurities were removed by additional preparative HPLC (Whatman Partisil 10, 500 x 9.4 mm, EtOAc/hexane 1:4, 5 mL/min, detection at 280 nm,  $t_r$  16.1 min) to yield 30.3 mg (21%) of the title compound as a glass:  $[\alpha]_D^{25} +16.2^\circ$ ,  $[\alpha]_{446}^{25} +19.4^\circ$  (EtOAc, c 12.3  $\text{g/L}^{-1}$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (two rotamers)  $\delta$  7.5-6.7 (m), 6.26 (s), 6.22 (s), 6.14 (s), 6.09 (s), 5.99 (s), 5.52 (s), 5.44 (s), 5.20-4.71 (m), 4.56, 4.37 (ABq,  $J = 12.5$  Hz), 4.12 (br), 3.90 (br s), 3.74 (br), 3.03, 2.95 (ABq, minor rotamer,  $J = 17$  Hz, both parts d with  $J = 2.5$  and 3.5 Hz, resp.), 2.92, 2.81 (ABq, major rotamer,  $J = 18$  Hz, B part d with  $J = 4.5$  Hz), 1.35 (s), 0.54 (s), 0.50 (s), -0.31 (s), -0.54 (s); IR (film) 2927, 1603, 1512, 1267, 1111, 734, 696  $\text{cm}^{-1}$ ; MS (ES)  $m/z$  1512.8, 1511.9, 1510.8, 1509.8, 1508.8 ( $M + \text{NH}_4^+$ ; calcd. for  $^{13}\text{C}^{12}\text{C}_9\text{H}_9\text{BrNO}_2\text{Si}/^{12}\text{C}_9\text{H}_9\text{BrNO}_2\text{Si}/^{13}\text{C}^{12}\text{C}_9\text{H}_9\text{BrNO}_2\text{Si}/^{12}\text{C}_9\text{H}_9\text{BrNO}_2\text{Si}$ : 1511.5/1510.5/1509.5/1508.5).

All human tumor cell lines were obtained from the American Type Culture Collection. Cells were grown as monolayers in IMEM containing 10% fetal bovine serum without antibiotics. The cells were maintained in a humidified, 5% CO<sub>2</sub> atmosphere at 37°C.

After trypsinization, the cells were counted and adjusted to a concentration of 1,000-2,000 cells per 100 mL. Cell proliferation was determined by plating the cells (1,000-2,000 cells/well) in a 96 well microtiter plate. After addition of 100µL cells per well, the cells were allowed to attach for 24 hours. At the end of the 24 hour period, various polyphenol derivatives were added at different concentrations to obtain dose response results. The polyphenols were dissolved in media at a 2 fold concentration and 100µL of each solution was added in triplicate wells. On consecutive days, the plates were stained with 50µL crystal violet (2.5 g crystal violet dissolved in 125 mL methanol, 375 mL water), for 15 min. The stain was removed and the plate was gently immersed into cold water to remove excess stain. The washings were repeated two more times, and the plates allowed to dry. The remaining stain was solubilized by adding 100µL of 0.1 M sodium citrate/50% ethanol to each well. After solubilization, the number of cells were quantitated on an ELISA plate reader at 540 nm (reference filter at 410 nm).

Cancer cell line growth at the end of four days was plotted as the percent growth of the control and is shown in Fig. 1(a)-(d) as bar graphs. Error bars represent +/- standard deviation of three replicate measurements. The data indicated that the monomer (epicatechin) and synthetic epicatechin dimer showed no cytotoxicity against the breast cancer cell lines investigated. However, the synthetic epicatechin dimer

stirring at room temperature with a solution of 0.1 g of  $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$  in 2 mL of water. The phases were separated, and the aqueous phase was extracted with 5 mL of  $\text{CH}_2\text{Cl}_2$ . Evaporation, filtration over silica gel (10 x 1.1 cm) with  $\text{EtOAc}/\text{CH}_2\text{Cl}_2/\text{hexane}$  1:6:3, and again evaporation gave 65 mg of a crude mixture which was separated by preparative TLC ( $\text{SiO}_2$ , 200 x 200 x 2 mm,  $\text{EtOAc}/\text{toluene}$  1:15, 2 developments) and additionally purified by preparative HPLC (Whatman Partisil 10, 500 x 9.4 mm,  $\text{EtOAc}/\text{hexane}$  1:4, 5 mL/min, detection at 280 nm). The major product obtained thereby was identical by NMR with the one obtained above:  $[\alpha]_D$ ,  $[\alpha]_{46}$  +0.6° ( $\text{EtOAc}$ , c 8.4 gL<sup>-1</sup>); <sup>1</sup>H NMR ( $\text{CDCl}_3$ , (two rotamers)  $\delta$  7.5-6.8 (m), 6.78 (d, J = 8 Hz), 6.74 (d, J = 1 Hz), 6.34 (s), 6.27 (dd, J = 1, 8 Hz), 6.19 (s), 6.16 (s), 6.02 (s), 5.56 (s), 5.36 (s), 5.2-4.95 (m), 4.9-4.7 (m), 4.60, 4.36 (ABq, J = 12 Hz), 4.33 (br), 4.11 (br), 3.99 (s), 3.80 (br), 3.08-2.80 (2 ABq, minor rotamer A part at 3.04, J = 17.5 Hz, B part not discernible; major rotamer at 2.96, 2.85, J = 18 Hz, B part d with J = 4.5 Hz), 1.66 (d, J = 5 Hz), 1.58 (d, J = 5 Hz), 1.40 (d, J = 3.5 Hz), 1.28 (partially overlapping with solvent-derived impurity); IR (film) 1604, 1512, 1266, 1117, 735, 696 cm<sup>-1</sup>; MS (ES) m/z 1398.6, 1397.6, 1396.6, 1395.6, 1394.6 (M + NH<sub>4</sub><sup>+</sup>; calcd. for <sup>13</sup>C<sup>12</sup>C<sub>35</sub>H<sub>77</sub><sup>81</sup>BrNO<sub>12</sub>/<sup>13</sup>C<sub>36</sub>H<sub>77</sub><sup>81</sup>BrNO<sub>12</sub>/<sup>13</sup>C<sup>12</sup>C<sub>35</sub>H<sub>77</sub><sup>79</sup>BrNO<sub>12</sub>/<sup>13</sup>C<sub>36</sub>H<sub>77</sub><sup>79</sup>BrNO<sub>12</sub>: 1397.5/1396.5/1395.5/1394.5).

## EXAMPLE 25

## Cytotoxic Activity

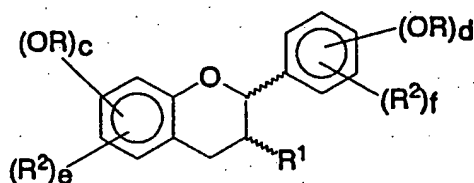
The epicatechin dimer bisgallate (abbreviated ECDG) and epicatechin trimer trisgallate (abbreviated ECTG) were screened for activity against certain breast cancer cell lines, and the results are presented graphically in Fig. 1(a)-(d).



## WE CLAIM:

1. A process for the production of a polyphenol oligomer, wherein said oligomer is comprised of monomeric units, each unit being comprised of a coupled polyphenol monomer, said process comprising the steps of:

(a) protecting each phenolic hydroxyl group of a first and a second polyphenol monomer with a protecting group to produce a first and second protected polyphenol monomer independently selected from monomers represented by the formula:



c is an integer from 1 to 3;

d is an integer from 1 to 4;

e is an integer from 0 to 2;

f is an integer from 0 to 2;

R<sup>1</sup> is H, OH or OR<sup>3</sup>;

R and R<sup>3</sup> are independently protecting groups;

and

R<sup>2</sup> is halo;

(b) functionalizing the 4-position of the first protected polyphenol monomer to produce a functionalized protected polyphenol monomer having the formula:

bisgallate and synthetic epicatechin trimer trisgallate elicited a cytotoxic effect equivalent to the pentamer and/or epigallocatechin gallate, especially at higher dosages.

5

It was surprisingly found that the dimer bisgallate and trimer trisgallate exhibited greater antineoplastic activity when compared to the underivatized dimer and trimer. These results indicate that gallation of the  
10 previously inactive cocoa procyanidin oligomers substantially increases the antineoplastic activity of the compounds. Thus, gallation of the dimer provides a compound which is useful for the uses as described in U.S. Patent Application No. 08/831,245 filed April 2,  
15 1997.

4. The process according to claim 1, wherein  $R^1$  is  $OR^3$  or  $R^4$  is  $R^5$  in the functionalized protected polyphenol monomer.

5. The process according to claim 4, wherein  $R^3$  is an alkyl silyl protecting group.

6. The process according to claim 2, wherein halo is bromo.

7. The process according to claim 6, wherein said protected polyphenol monomer is a brominated protected epicatechin or brominated protected catechin.

8. The process according to claim 7, wherein said epicatechin is an 8-bromoepicatechin or an 8-bromocatechin.

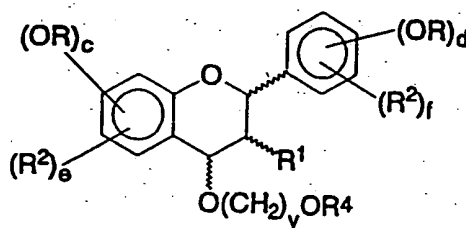
9. The process according to claim 7, wherein said epicatechin is a 6,8,6'-tribromo-epicatechin or a 6,8,6'-tribromo-catechin.

10. The process according to claim 2, wherein at least one  $R^2$  is halo for said functionalized protected polyphenol monomer.

11. The process according to claim 10, wherein said functionalizing and coupling steps are repeated to form a halogenated polyphenol oligomer having 3 to 18 monomeric units.

12. The process according to claim 10, wherein halo is bromo.

13. The process according to claim 12, wherein said brominated functionalized polyphenol



wherein

c is an integer from 1 to 3;

d is an integer from 1 to 4;

e is an integer from 0 to 2;

f is an integer from 0 to 2;

y is an integer from 2 to 6;

R<sup>1</sup> is H, OH or OR<sup>3</sup>;

R<sup>4</sup> is H or R<sup>5</sup>;

R, R<sup>3</sup> and R<sup>5</sup> are independently protecting groups; and

R<sup>2</sup> is halo;

(c) coupling the second protected polyphenol monomer with the functionalized protected polyphenol monomer to produce a protected polyphenol dimer as the polyphenol oligomer; and

(d) optionally repeating the functionalization and coupling steps to form the polyphenol oligomer having n monomeric units, wherein n is an integer from 3 to 18.

2. The process according to claim 1, wherein at least one R<sup>2</sup> is halo in at least one of the protected polyphenol monomers.

3. The process according to claim 1, wherein at least one R<sup>2</sup> is halo for said second protected polyphenol monomer.

21. The process according to claim 1, further comprising removing the protecting group from the phenolic hydroxyl groups of the polyphenol oligomer to produce an unprotected polyphenol oligomer.

22. The process according to claim 1, wherein the R is benzyl.

23. The process according to any of claims 1 and 21, further comprising the step of forming a derivative of the polyphenol oligomer by esterifying the polyphenol oligomer at the 3-position of at least one monomeric unit, to produce an esterified polyphenol oligomer.

24. The process according to any of claims 1 and 21, further comprising the step of forming a derivative of the polyphenol oligomer by glycosylating the polyphenol oligomer at the 3-position of at least one monomeric unit, to produce a glycosylated polyphenol oligomer.

25. The process according to claim 23, wherein the 3-position of at least one monomeric unit is converted to a derivative group selected from the group consisting of -OC(O)aryl, -OC(O)-substituted aryl, -OC(O)-styryl, and -OC(O)-substituted styryl; wherein said substituted aryl or substituted styryl contains at least one substituent selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy.

26. The process according to claim 23, wherein the 3-position of at least one monomeric unit is converted to a derivative group derived from an acid

monomer is a brominated functionalized epicatechin or a brominated functionalized catechin.

14. The process according to claim 13, wherein said epicatechin is an 8-bromoepicatechin or an 8-bromocatechin.

15. The process according to claim 13, wherein said epicatechin is a 6,8,6'-tribromo-epicatechin or a 6,8,6'-tribromo-catechin.

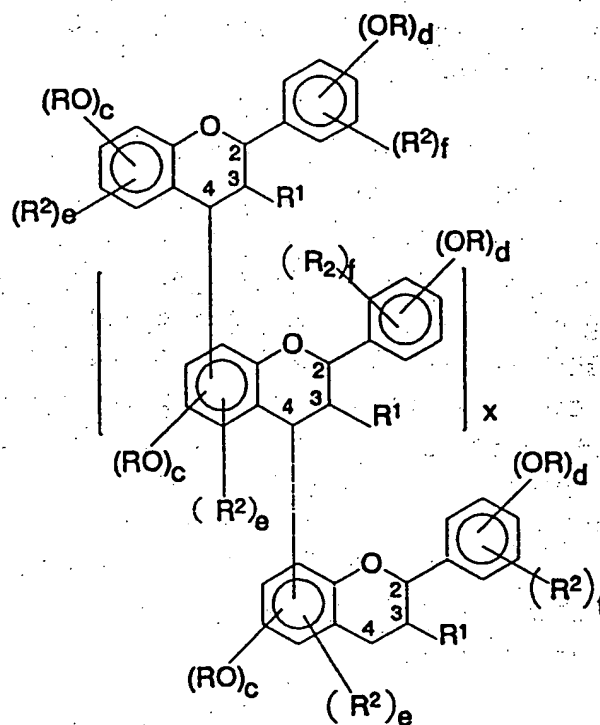
16. The process according to claim 1, wherein n is an integer from 5 to 12.

17. The process according to claim 1, further comprising halogenating the polyphenol oligomer.

18. The process according to claim 1, wherein the step of functionalizing the 4-position of the protected polyphenol monomer comprises oxidatively functionalizing the 4-position of the protected polyphenol monomer using a quinone oxidizing agent in the presence of a diol.

19. The process according to claim 18, wherein the diol is ethylene glycol and y is 2.

20. The process according to claim 1, wherein R is independently C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl, substituted benzyl, a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, and, when c or d is 2 and are adjacent, methylene, diphenylmethylene or substituted diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkoxy.



wherein:

x is an integer from 0 to 16;

c is independently an integer from 1 to 3;

d is independently an integer from 1 to 4;

e is independently an integer from 0 to 2;

f is independently an integer from 0 to 2;

R is independently selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, benzyl, substituted benzyl, a silyl moiety containing C<sub>1</sub>-C<sub>6</sub> alkyl or aryl substituents, and, when c or d is 2 and are adjacent, methylene, diphenylmethylene or substituted diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkoxy; and

selected from the group consisting of caffeic, cinnamic, coumaric, ferulic, gallic, hydroxybenzoic and sinapic acids.

27. The process according to claim 24, wherein the 3-position of at least one monomeric unit is converted to a derivative group selected from the group consisting of -O-glycoside or an -O-substituted glycoside, wherein the substituted glycoside is substituted by -C(O)aryl, -C(O)-substituted aryl, -C(O)-styryl, or -C(O)-substituted styryl; wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> haloalkyl, C<sub>1</sub>-C<sub>6</sub> haloalkoxy, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, and C<sub>3</sub>-C<sub>8</sub> cycloalkoxy.

28. The process according to claim 27, wherein the glycoside is selected from the group consisting of glucose, galactose, xylose, rhamnose and arabinose.

29. The process according to any of claims 1 and 21, providing the polyphenol oligomer having the formula:

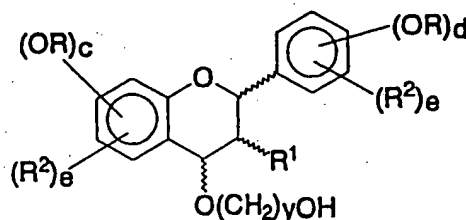


$R^1$  is selected from the group consisting of hydrogen, hydroxy, an -O-glycoside, an -O-substituted glycoside, -OC(O)-aryl, -OC(O)-substituted aryl, -OC(O)-styryl, and -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, or -C(O)-substituted styryl; and

$R^2$  is halo;

wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy,  $C_3$ - $C_8$  cycloalkyl, and  $C_3$ - $C_8$  cycloalkoxy.

31. A compound of the formula:



wherein

$c$  is an integer from 1 to 3;

$d$  is an integer from 1 to 4;

$e$  is an integer from 0 to 2;

$f$  is an integer from 0 to 2;

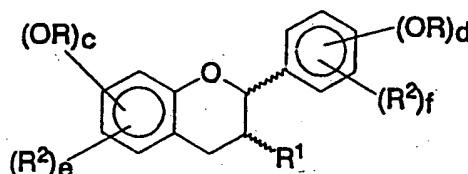
$y$  is an integer from 2 to 6;

$R$  is selected from the group consisting of hydrogen,  $C_1$ - $C_6$  alkyl, benzyl, substituted benzyl, a silyl moiety containing  $C_1$ - $C_6$  alkyl or aryl substituents, and, when  $c$  or  $d$  is 2 and are adjacent, methylene, diphenylmethylene or substituted diphenylmethylene, wherein said substituted benzyl or each substituted phenyl may contain substituents

$R^1$  is selected from the group consisting of hydrogen, an O-glycoside, an -O-substituted glycoside, -OC(O)aryl, -OC(O)-substituted aryl, -OC(O)-styryl, and -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)aryl, -C(O)-substituted aryl, -C(O)-styryl, -C(O)-substituted styryl; wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  haloalkoxy,  $C_3$ - $C_6$  cycloalkyl, and  $C_3$ - $C_6$  cycloalkoxy; and

$R^2$  is halo.

30. A compound of the formula:



wherein

$c$  is an integer from 1 to 3;

$d$  is an integer from 1 to 4;

$e$  is an integer from 0 to 2;

$f$  is an integer from 0 to 2;

$R$  is selected from the groups consisting of hydrogen,  $C_1$ - $C_6$  alkyl, benzyl, substituted benzyl, a silyl moiety containing  $C_1$ - $C_6$  alkyl or aryl substituents, and, when  $c$  or  $d$  is 2 and are adjacent, methylene, diphenylmethylenes or substituted diphenylmethylenes, wherein said substituted benzyl or each substituted phenyl may contain substituents selected from the group consisting of halo, nitro, cyano, aryl,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  haloalkyl,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  haloalkoxy,  $C_3$ - $C_6$  cycloalkyl,  $C_3$ - $C_6$  cycloalkoxy;

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a bond for an additional monomeric unit in position 4 has alpha or beta stereochemistry;

X, Y and Z are selected from the group consisting of monomeric unit A, hydrogen, and a sugar, with the provisos that as to the at least one terminal monomeric unit, bonding of the additional monomeric unit thereto is at position 4 and optionally Y = Z = hydrogen;

the sugar is optionally substituted with a phenolic moiety, and

pharmaceutically acceptable salts, derivatives thereof, and oxidation products thereof; which process comprises:

(a) protecting each phenolic hydroxyl group of a (+)-catechin or of a (-)-epicatechin with a protecting group to produce a protected (+)-catechin or a protected (-)-epicatechin;

(b) functionalizing the 4-position of the protected (+)-catechin or of the protected (-)-epicatechin or of a mixture thereof to produce a functionalized protected (+)catechin, a functionalized protected (-)-epicatechin or a functionalized protected mixture thereof;

(c) coupling the protected (+)-catechin or the protected (-)-epicatechin with the functionalized protected (+)catechin or the functionalized protected (-)-epicatechin or mixtures thereof to produce a protected polyphenol oligomer;

(d) removing the protecting group from the phenolic hydroxyl groups of the polyphenol oligomer to produce an unprotected polyphenol oligomer; and

(e) optionally forming the derivative of the protected or unprotected polyphenol oligomer to produce a derivatized polyphenol oligomer.

33. The process according to claim 32, wherein n is 5.

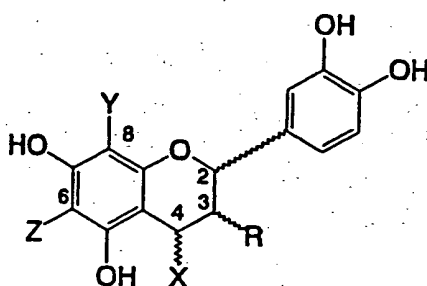
selected from the group consisting of halo, nitro, cyano, aryl,  $C_1-C_6$  alkyl,  $C_1-C_6$  haloalkyl,  $C_1-C_6$  alkoxy,  $C_1-C_6$  haloalkoxy,  $C_3-C_8$  cycloalkyl, and  $C_3-C_8$  cycloalkoxy;

$R^1$  is selected from the group consisting of hydrogen, hydroxy, an -O-glycoside, an -O-substituted glycoside, -OC(O)-aryl, -OC(O)-substituted aryl, -OC(O)-styryl, and -OC(O)-substituted styryl; wherein the substituted glycoside is substituted by -C(O)-aryl, -C(O)-substituted aryl, -C(O)-styryl, -C(O)-substituted styryl; and

$R^2$  is halo;

wherein said substituted aryl or substituted styryl may contain the substituents selected from the group consisting of halo, hydroxyl, nitro, cyano, amino, thiol, methylenedioxy,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy,  $C_1-C_6$  haloalkyl,  $C_1-C_6$  haloalkoxy,  $C_3-C_8$  cycloalkyl, and  $C_3-C_8$  cycloalkoxy.

32. A process for the production of a polymeric compound of the formula  $A_n$ , wherein A is a monomer of the formula:

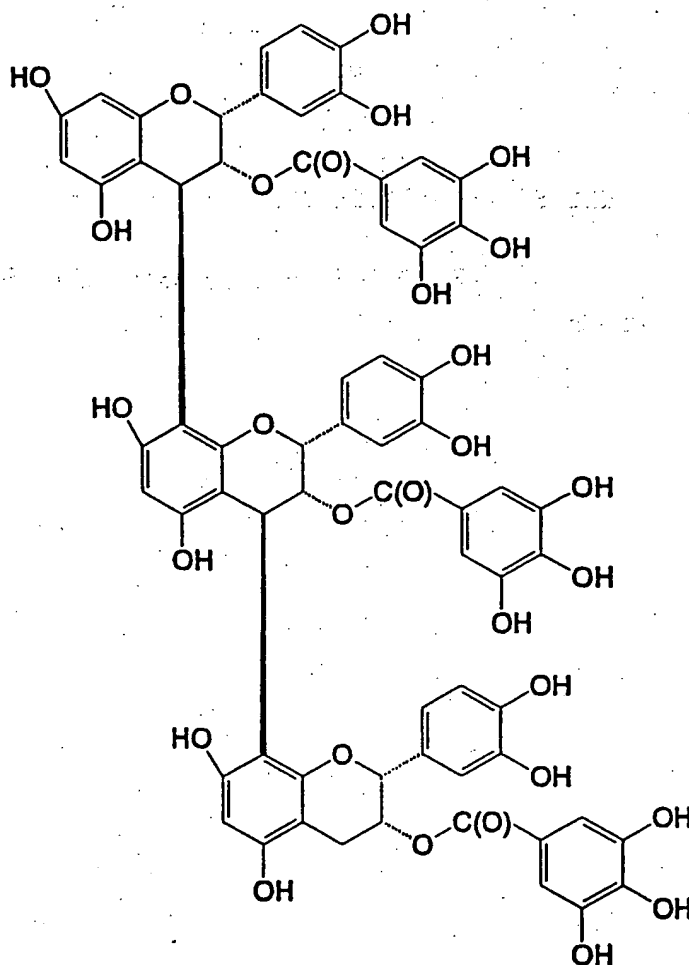


wherein n is an integer from 3 to 18, such that there is at least one terminal monomeric unit A, and a plurality of additional monomeric units;

R is 3-( $\alpha$ )-OH, 3-( $\beta$ )-OH, 3-( $\alpha$ )-O-sugar, or 3-( $\beta$ )-O-sugar;

bonding of adjacent monomers takes place between position 4 and positions 6 or 8;

39. A pharmaceutical composition comprising a compound of the formula:



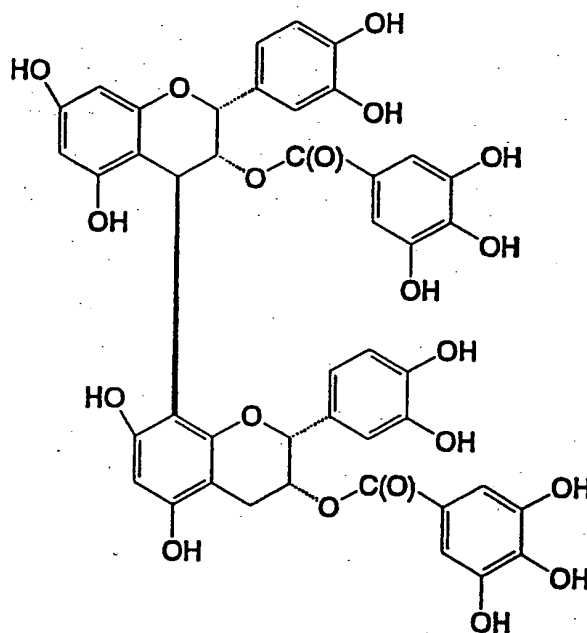
40. A method for treating a subject in need of treatment with an anticancer agent comprising administering an effective amount to the subject a composition as claimed in claim 39.

41. The method of claim 40, wherein said cancer is breast cancer.

34. The process according to claim 32, wherein the sugar is selected from the group consisting of glucose, galactose, xylose, rhamnose and arabinose.

35. The process according to claim 32, wherein the phenolic moiety is selected from the group consisting of caffeic, cinnamic, coumaric, ferulic, gallic, hydroxybenzoic and sinapic acids.

36. A pharmaceutical composition comprising a compound of the formula:



and a pharmaceutically acceptable carrier or excipient.

37. A method for treating a subject in need of treatment with an anticancer agent comprising administering an effective amount to the subject a composition as claimed in claim 36.

38. The method of claim 37, wherein said cancer is breast cancer.

# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 98/21392

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D311/62 C07D311/60 C07D311/32 C07H17/06 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 57, no. 31, 1962 Columbus, Ohio, US; abstract no. 3398b, E.J. KEOGH ET AL.: "A NEW SYNTHESIS OF FLAVANS." column 2; XP002093431 see abstract & CHEM. IND., 1961, page 2100 LONDON	1
X	---	30
X	DE 15 18 003 A (MERCK) 30 January 1969 see claims; examples 7,9 ---	30
X	EP 0 039 844 A (ZYMA) 18 November 1981 see page 1 - page 16 ---	30
	--- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 February 1999

Date of mailing of the international search report

02/03/1999

Name and mailing address of the ISA

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Authorized officer

Francois, J

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 98/21392

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 216 936 A (TSUMURA JUNTENDO) 8 April 1987 see the whole document	1, 36, 39
A	WO 90 13304 A (CARIEL) 15 November 1990 see page 6 - page 11; claims	1, 36-39
A	CHEMICAL ABSTRACTS, vol. 107, no. 26, 1987 Columbus, Ohio, US; abstract no. 6996d, page 643; XP002093432 see abstract & JP 06 248677 A (NIPPON SHINYAKU) 3 March 1987	1, 36, 39
A	CHEMICAL ABSTRACTS, vol. 100, no. 17, 1984 Columbus, Ohio, US; abstract no. 136144r, page 398; XP002093433 see abstract & JP 58 154571 A (NIPPON SHINYAKU) 14 September 1983	1, 36, 39
P, X	WO 97 36597 A (MARS) 9 October 1997 see claims; figure 38B	1, 36-39



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/21392

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 37, 38, 40, 41  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 37, 38, 40, 41  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No.  
PCT/US 98/21392

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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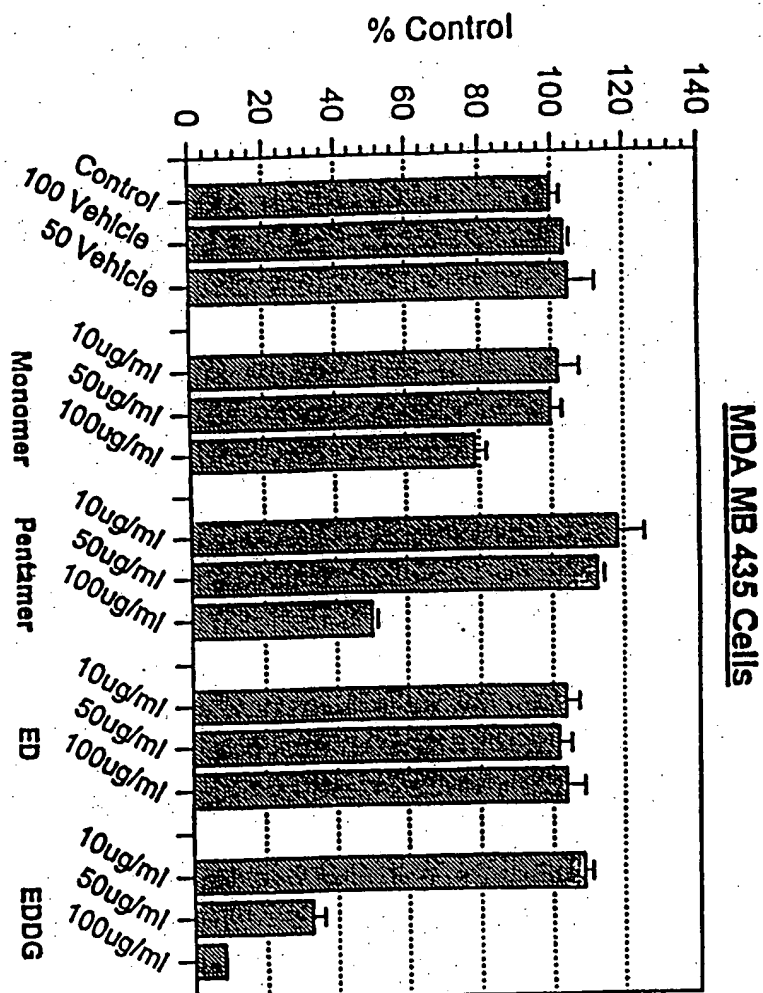


FIG. 1(b)

